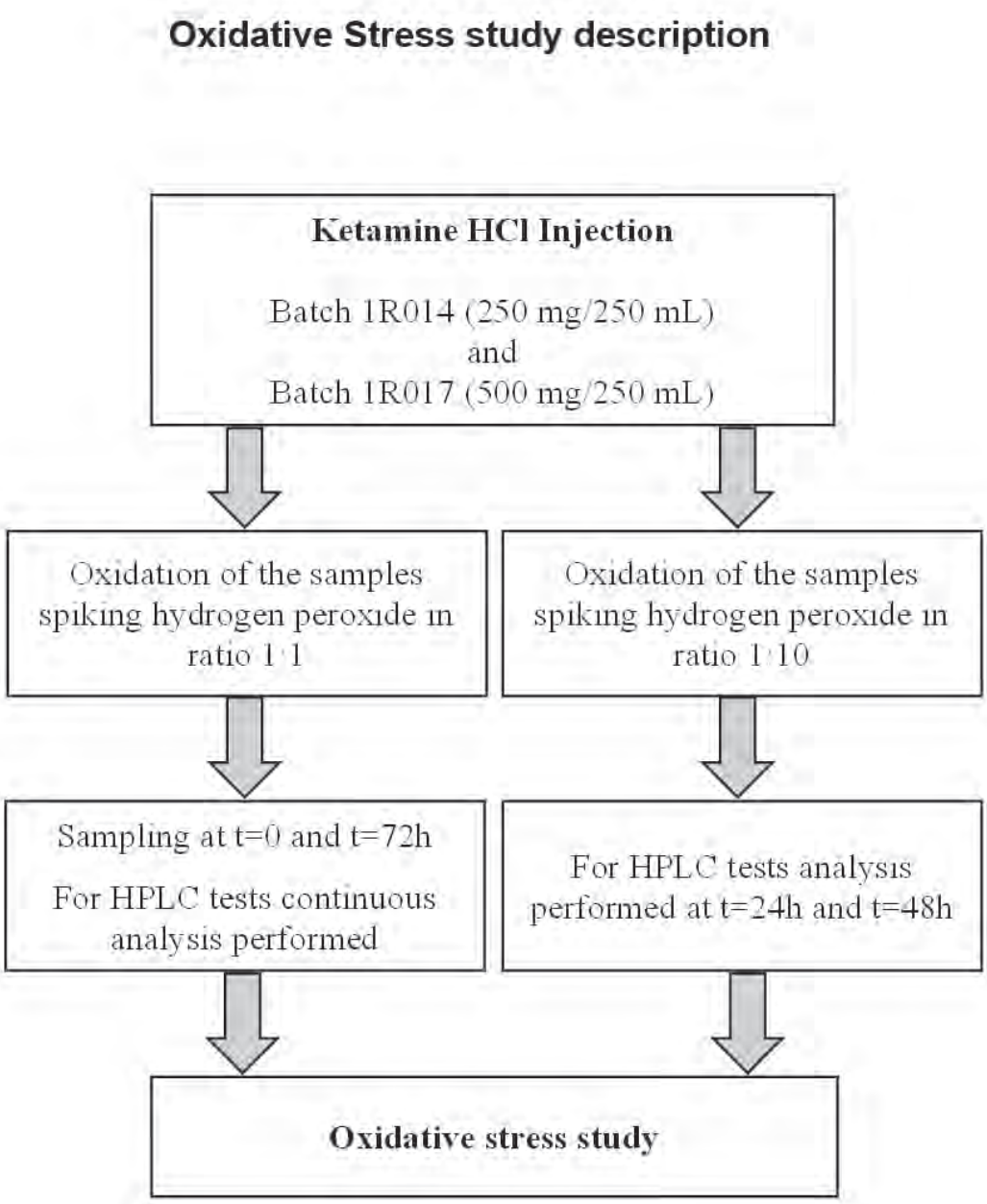

Oxidative Stress study description
Ketamine HCl Injection
Batch 1R014 (250 mg/250 mL)
and
Batch 1R017 (500 mg/250 mL)
Oxidation of the samples spiking hydrogen peroxide in ratio 1:1
Oxidation of the samples spiking hydrogen peroxide in ratio 1:10
Sampling at t=0 and t=72h
For HPLC tests continuous analysis performed
For HPLC tests analysis performed at t=24h and t=48h
Oxidative stress study

Fig. 1

Acid Alkaline stress study description

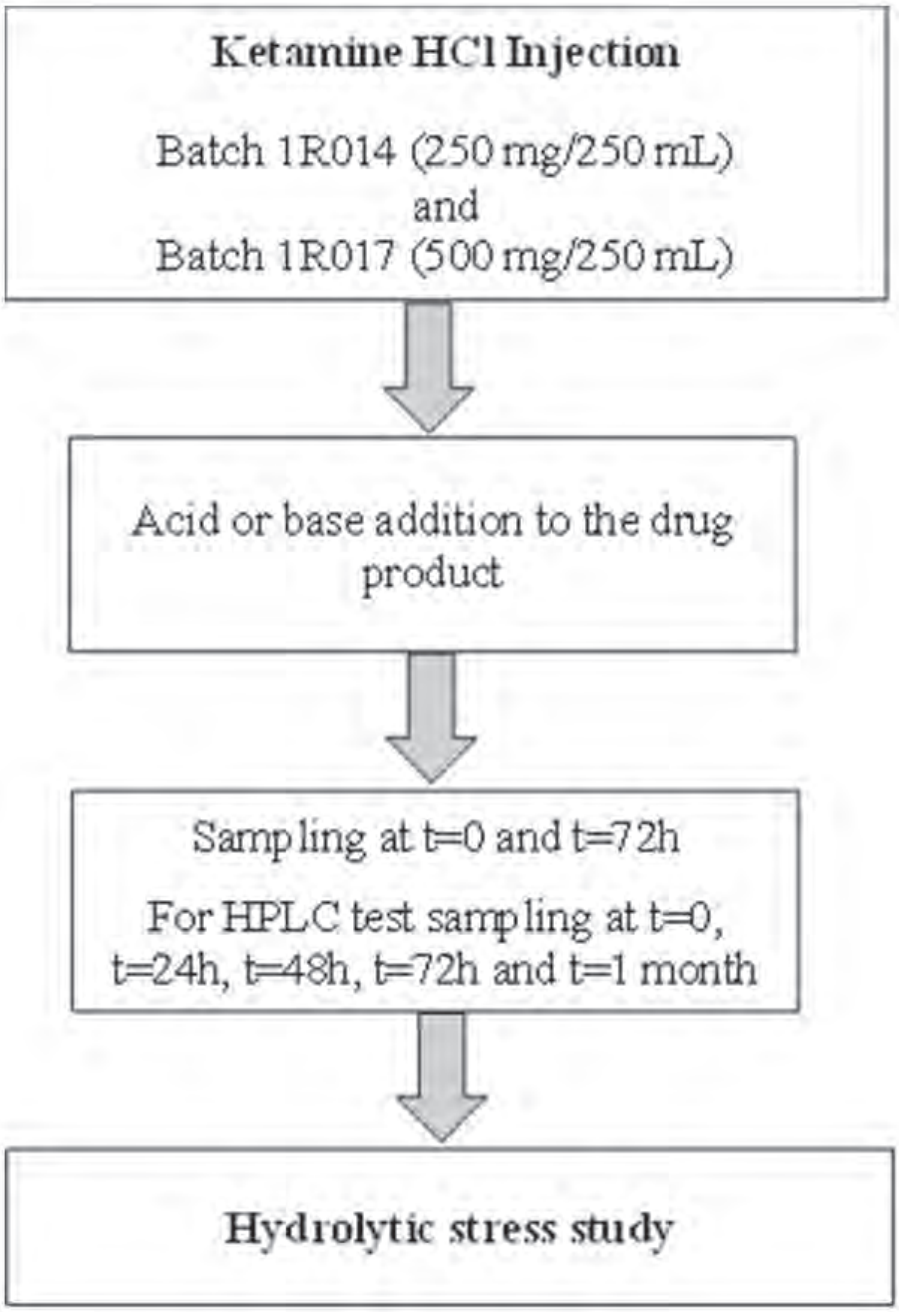


Fig. 2

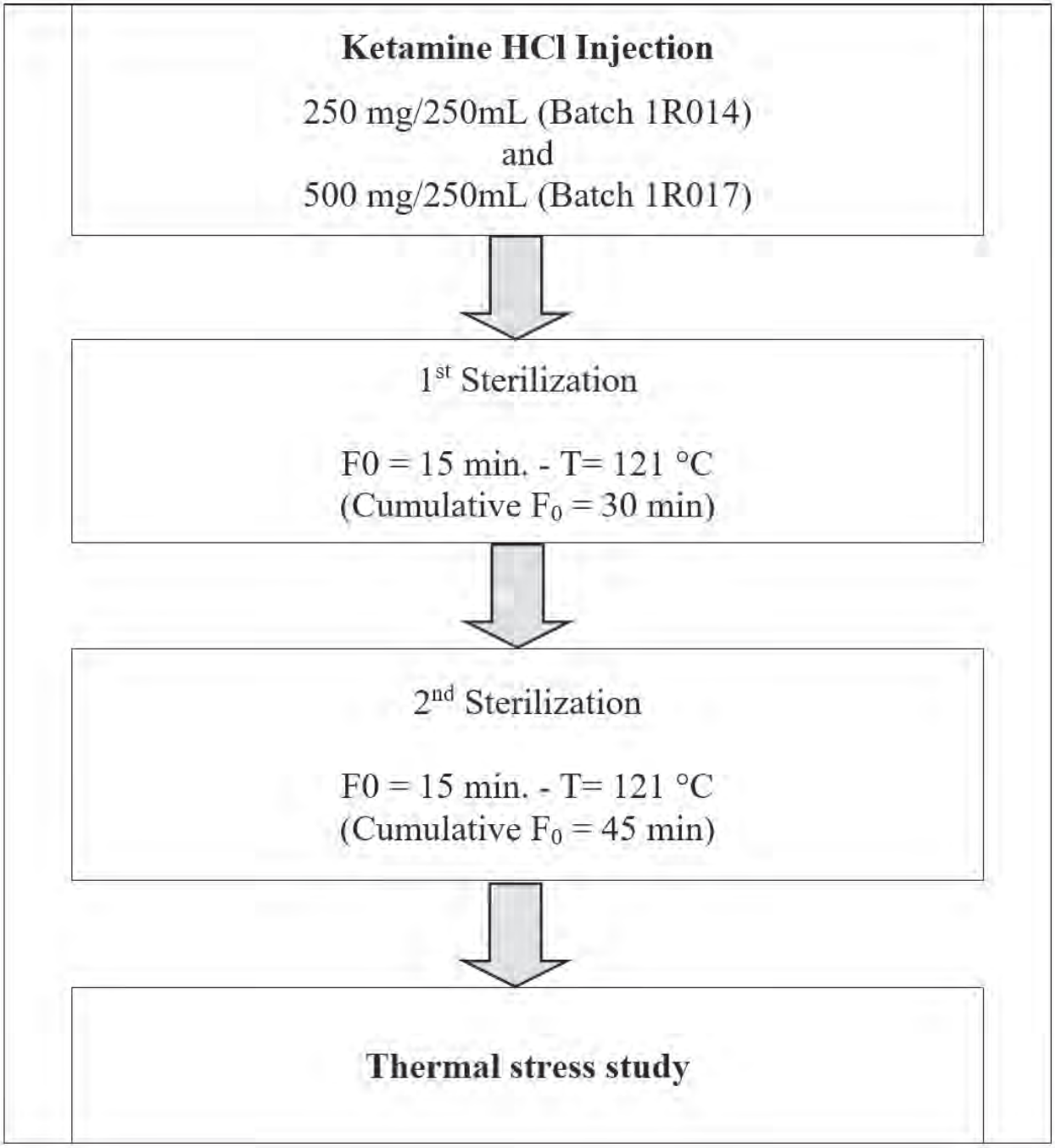

Ketamine HCl Injection
250 mg/250mL (Batch 1R014)
and
500 mg/250mL (Batch 1R017)
1st Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 30 min)
2nd Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 45 min)
Thermal stress study

Fig. 3

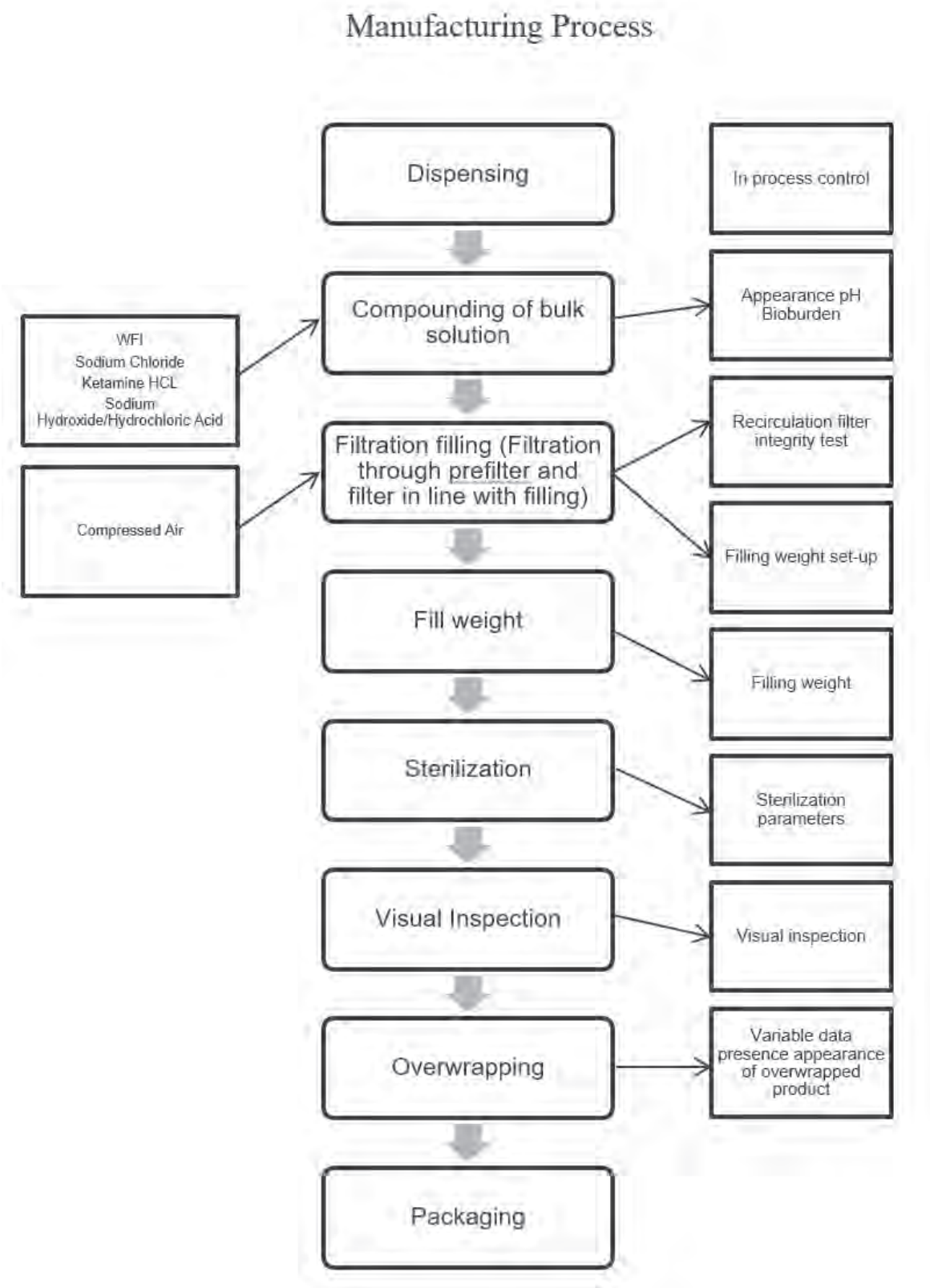

Manufacturing Process
Dispensing
In process control
Compounding of bulk solution
Appearance pH Bioburden
WFI
Sodium Chloride
Ketamine HCL
Sodium Hydroxide/Hydrochloric Acid
Filtration filling (Filtration through prefilter and filter in line with filling)
Recirculation filter integrity test
Compressed Air
Filling weight set-up
Fill weight
Filling weight
Sterilization
Sterilization parameters
Visual Inspection
Visual inspection
Overwrapping
Variable data presence appearance of overwrapped product
Packaging

Fig. 4

Graph 1: Ketamine Injection 1 mg/mL Dissolution Assay

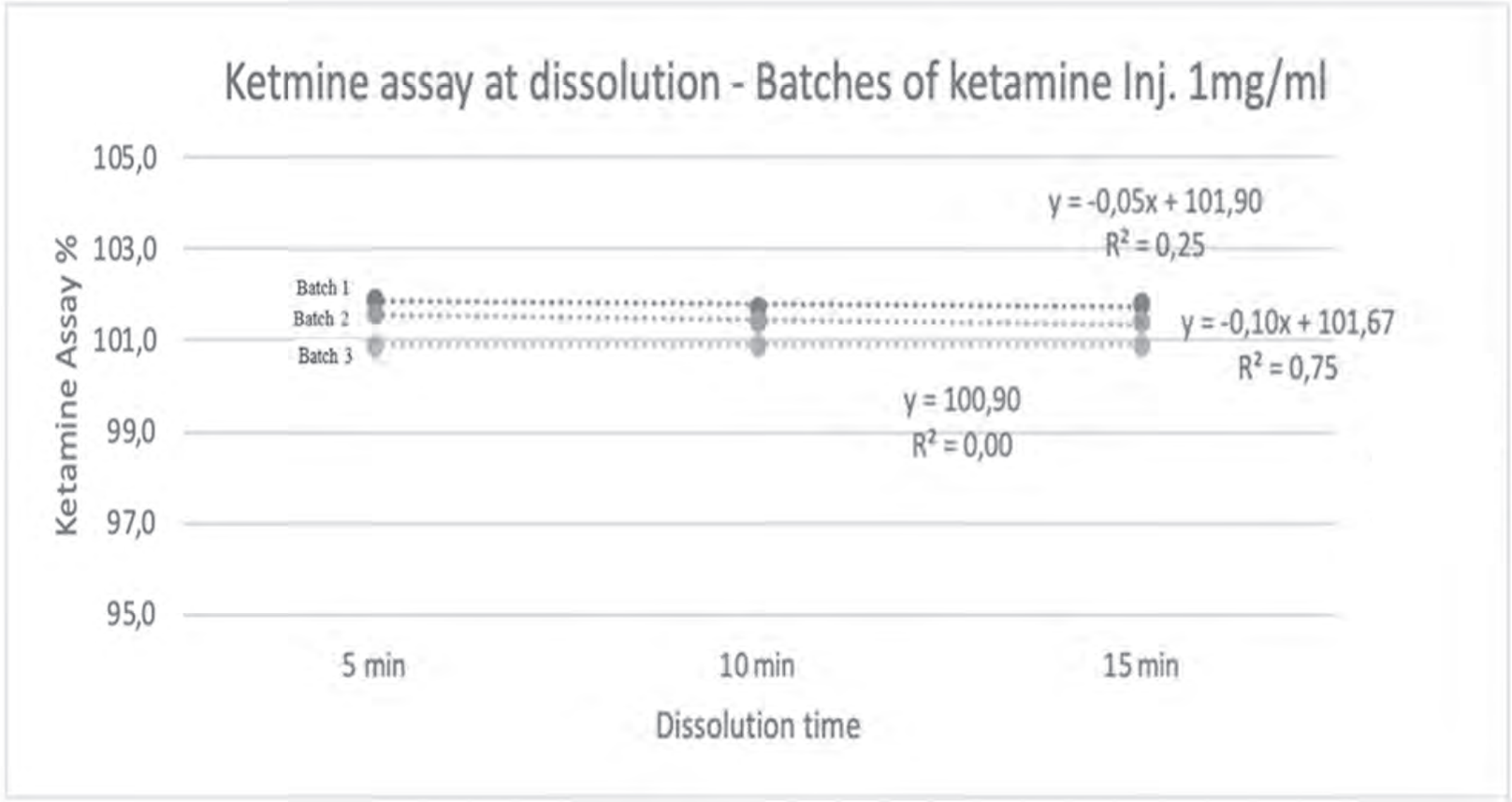


Fig. 5

Graph 2: Ketamine Injection 2 mg/mL Dissolution Assay

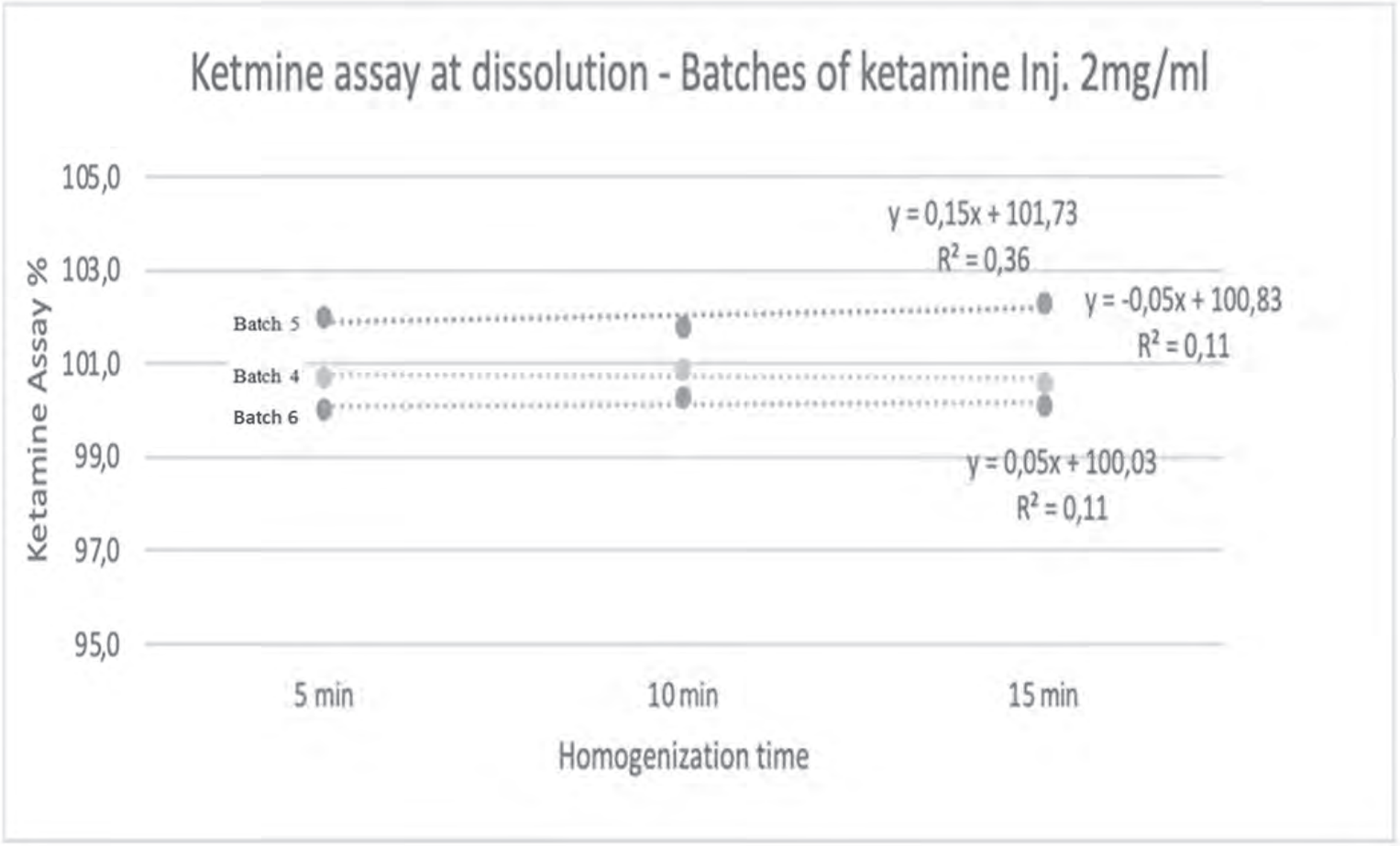


Fig. 6

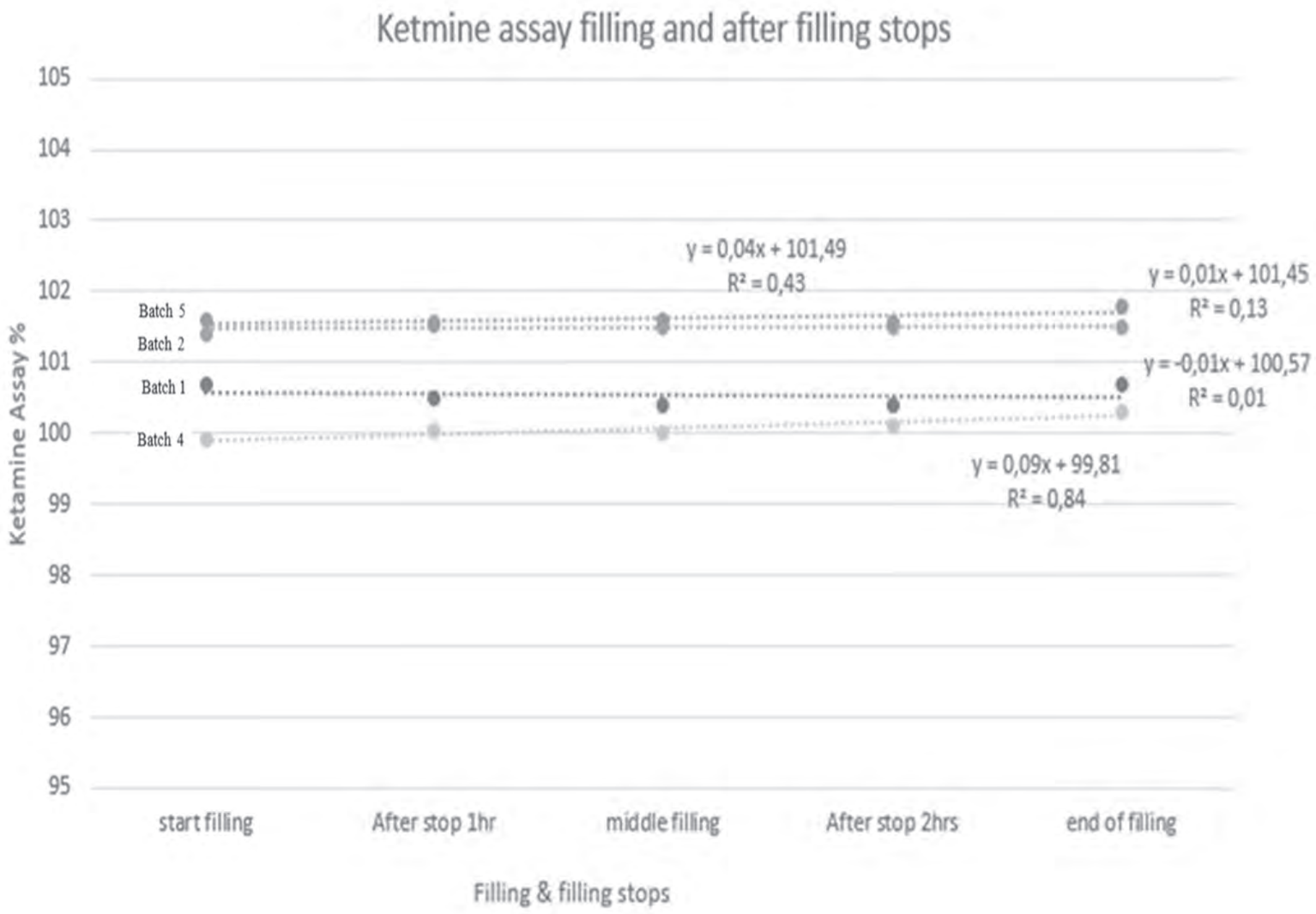

Ketmine assay filling and after filling stops
105
104
103
102
101
100
99
98
97
96
95
Ketamine Assay %
Batch 5
Batch 2
Batch 1
Batch 4
y = 0,04x + 101,49
R² = 0,43
y = 0,01x + 101,45
R² = 0,13
y = -0,01x + 100,57
R² = 0,01
y = 0,09x + 99,81
R² = 0,84
start filling
After stop 1hr
middle filling
After stop 2hrs
end of filling
Filling & filling stops

Fig. 7

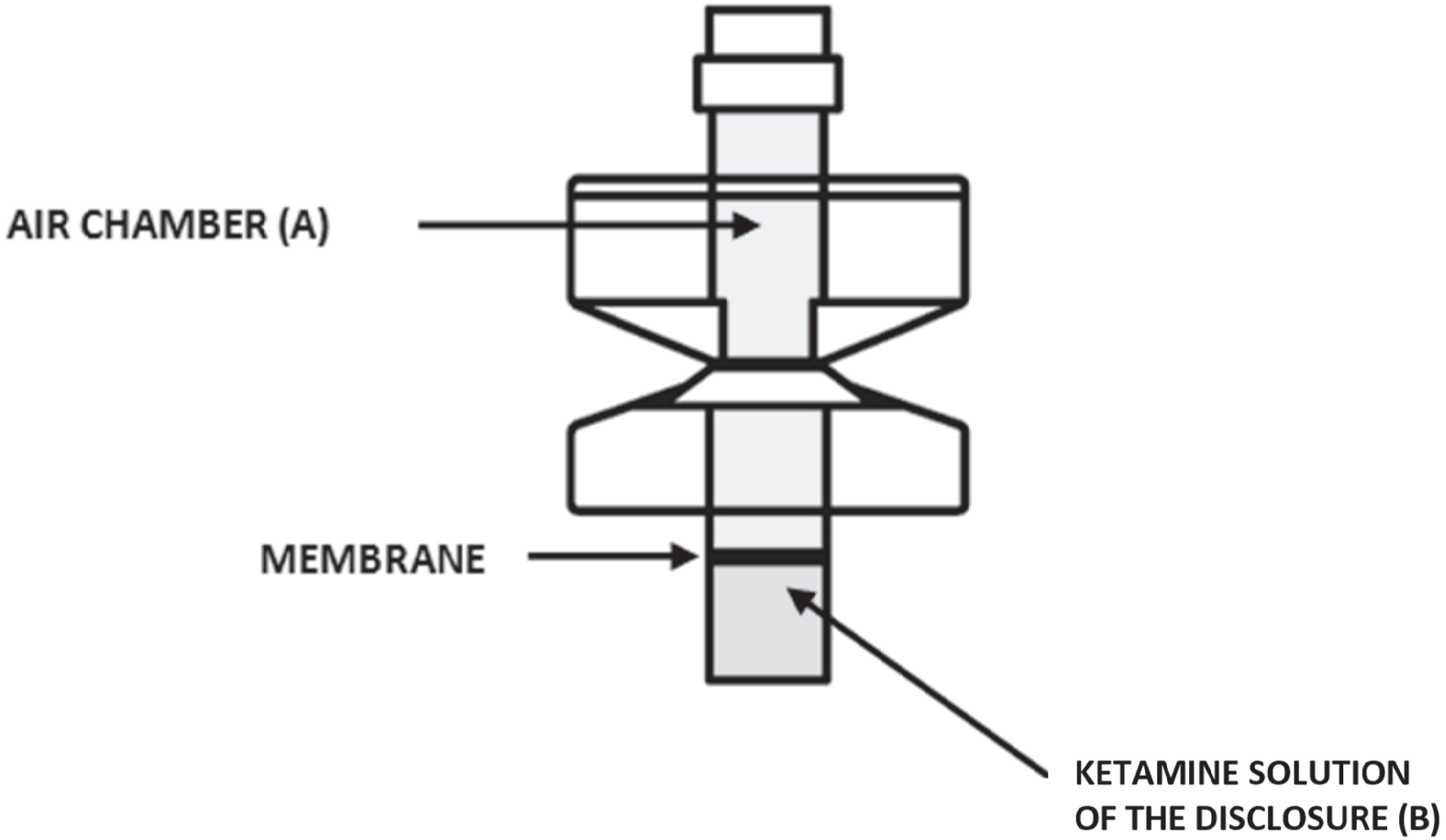

AIR CHAMBER (A)
MEMBRANE
KETAMINE SOLUTION
OF THE DISCLOSURE (B)

Fig. 8

DocCode - SCORE

Placeholder Sheet for Supplemental Content

Application Number: 18770514 Document Date: 07/11/2024

The presence of this form indicates that the following document type was received in electronic format on the date identified above. This document is stored separately from the typical case contents which are stored in image format.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded and no paper documents or physical media exist.

- Drawing

At the time of document entry (noted above):

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- External customers may access this supplemental content via Patent Center.

Form Revision Date: March 1, 2024

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18770514 Document Date: 07/11/2024

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- USPTO employees may access SCORE content via DAV or via the SCORE web page.
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Form Revision Date: March 1, 2019

READY-TO-USE KETAMINE PREMIX FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. provisional application number 63/513,225, filed July 12, 2023 the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to ready-to-use, sterile, premixed formulations of ketamine, or a pharmaceutically acceptable salt thereof, that does not include benzethonium chloride, is chemically stable for approximately 24 months or more, and can be used, for example, to treat a subject in need of anesthesia for a diagnostic or a surgical procedure.

BACKGROUND

[0003] Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride. Ketamine is a noncompetitive, high affinity NMDA receptor antagonist. Ketamine's mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system. Ketamine has been used as an anesthetic agent.

[0004] Most preparations of ketamine contain equal (1:1) concentrations of its two enantiomers: S (+) ketamine and R (−) ketamine. Ketamine formulations that are commercially available and approved by the FDA in the U.S. currently contain benzethonium chloride added as a preservative.

[0005] Ketamine can be administered to a patient in a variety of ways. For example, ketamine can be used as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Alternatively, ketamine can be administered for the induction of anesthesia prior to the administration of other general anesthetic agents or as a supplement to other anesthetic agents.

[0006] The container closure system of a product intended for parenteral use has to ensure continuous compliance with the storage and handling specifications throughout the product shelf life to maintain functionality and drug delivery accuracy. Several factors have to be considered when choosing the right container closure system for an injectable product, such as drug product formulation properties, dosage, type of application, stability, stability when subjected to extreme

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conditions (such as during terminal sterilization), sterility, container closure integrity, storage conditions and duration, and end-user friendliness. Thus, there is a need to develop container closure systems that are appropriate for specific injectable products that maintains functionality and drug delivery accuracy.

[0007] Vials are the most common primary packaging for administration of ketamine injectables on the market in the U.S. Such vials contain concentrated ketamine solution. For intravenous (IV) administration, it is necessary to introduce the ketamine solution into an infusion container containing a suitably diluted IV solution. Thus, to date, ketamine has been provided as a concentrate that must be diluted with sterile water for injection (WFI), a sodium chloride solution, saline, or a dextrose in water solution prior to administration to a patient and must be used immediately after dilution. If the entire vial is not required, then the vial must still be disposed of as the vials are single use only.

[0008] There is no available single intravenous dosage form that provides a sterile, ready-to–use, stable, liquid formulation of ketamine that can be administered without any manipulation to a patient in need thereof, thereby avoiding a compromise with the sterility, an error in dosing accuracy and/or in medicament preparation etc. There is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine which can be administered to a patient in need thereof without deviation or manipulations and while preserving the sterility of the product, and optionally with a provision for administering along with other medicaments for combination or sequential therapy, if needed or desired. There also is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine that does not contain a preservative or antimicrobial such as benzethonium chloride. Preferably the shelf-life of the sterile, ready to use ketamine solution will be 24 months or more at room temperature.

SUMMARY OF THE INVENTION

[0009] In the present invention, the inventors have overcome multiple problems of prior art ketamine formulations, such as additional costs and inconvenience; the risk of potential contamination due to inadvertent medical error; long-term storage of a ready to use dosage of a stable, preservative-free ketamine solution. The inventors have developed a sterile, stable liquid formulation of ketamine in an infusion container that is at a ready to use concentration. For plastic materials being considered for use as primary packing materials for the infusion container, the challenge has been to develop packaging that is compatible with the contents, minimizes

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extractables/leachables, are solvent-resistant, and are durable. The packaging of a pharmaceutical product should desirably be stable and mutually compatible under terminal sterilization conditions, as packaging materials and terminal sterilization can affect the condition of different formulations. A sterile ready to use ketamine formulation in an infusion container avoids the expense, inconvenience, delay, and risk of contamination, and provides significant advantages over currently available concentrated formulations. Additionally, the inventors have beneficially developed a formulation of ketamine that is shelf-stable in an infusion container for greater than three months, and preferably for 24 months or more, without the use of preservatives or antimicrobials such as benzethonium chloride.

[00010] The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an intravenous bag or other infusion container. The ready-to-use premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, e.g., in a ready-to-use infusion bag (also referred to as a "ready-to-use bag").

[00011] In one aspect, the ketamine product of the disclosure is a ready-to-use, sterile, infusion bag comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection. In one aspect, the ketamine product is terminally sterilized. In one aspect, the ketamine product comprise a sterile aqueous ketamine solution that is aseptically filled, for example, the sterile aqueous ketamine solution is filled under aseptic conditions into a sterile infusion bag. In one aspect, the ketamine product of the disclosure is free of a preservative or antimicrobial such as benzethonium chloride.

[00012] In one aspect, the ready-to-use, sterile, infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

[00013] In one aspect, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3.5 to 5.5.

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[00014] In one aspect, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, and a complexing agent. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

[00015] In one aspect, the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution is formulated as a total volume of about 50- 500 mL.

[00016] In one aspect, the ready-to-use, sterile, infusion bag comprising aqueous ketamine solution without benzethonium chloride comprises at least one port. In one aspect, the ready to use terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride comprises at least one tube port closed with a closure. In certain aspects, the closure is a twist off closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the twist off closure comprises a membrane that creates a barrier, splitting the twist-off closure in two parts. In certain aspects, the twist off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure as illustrated in Figure 8. In certain aspects, the twist off closure comprises at least one layer of polypropylene. In certain aspects, the closure is a rubber stopper. In certain aspects, the twist off closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises a plastic material. In certain aspects, the closure is a cap. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer. In certain aspects, the tube port comprises one or more layers of a plastic material.

[00017] In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible multilayer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, filling, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials

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such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof etc. In certain aspects, the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a flexible multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a flexible multilayer film in which certain layers are comprised of different polymers or polymer blends from other layers. In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible single layer film.

[00018] In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a flexible intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use terminally sterilized aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

[00019] In one aspect, the infusion container may be enclosed in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

[00020] In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized by autoclaving. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using steam sterilization. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using heat sterilization. In one aspect, the ready-to-use infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by radiation. In one aspect, the ready-to-use, infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by chemical sterilization (e.g., ethylene oxide).

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[00021] In one aspect, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than three months at room temperature. In some aspects, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than six months, greater than twelve months, greater than eighteen months, or greater than twenty-four months at room temperature. In one aspect, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15–30°C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, terminally sterilized, infusion container.

[00022] In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 6000 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 μm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months.

[00023] In one aspect, the impurities in the ready-to-use, sterile, infusion bag comprising a aqueous ketamine solution without benzethonium chloride total not more than 1%, not more than 0.4%, not more than 0.3%, not more than 0.2%, not more than 0.15%, or not more than 0.05%, or not more than 0.01%.

[00024] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25%

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RH for 6 months is greater than 98%, greater than 99%, or greater than 99.5%, or greater than 99.9%, or greater than 99.95%.

[00025] In one aspect, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In one aspect, the bacterial endotoxin in the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

[00026] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater.

[00027] In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized, infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (iv); (vii) overwrapping the terminally sterilized infusion bag of step (vi) with an overwrap. In certain aspects, the terminal sterilization is conducted by autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for about 15 minutes. In certain

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aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat ensures a hermetic seal between the tube port and the film and the tube port and closure.

[00028] In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution from the ready-to-use, sterile infusion bag to the subject without diluting the ketamine solution; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

[00029] In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

[00030] In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[00031] Fig. 1 shows the steps and specifications of the oxidative stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine product of the disclosure"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were spiked with hydrogen peroxide at different ratios (1:1 and 1:10). HPLC tests were performed to determine the effects of oxidative stress on the ketamine HCL injection product.

[00032] Fig. 2 shows the steps and specifications of the acid alkaline stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). An acid or base was added to two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively). HPLC tests were performed to determine the effects of hydrolytic stress on the ketamine HCL injection product.

[00033] Fig. 3 shows the steps and specifications of the thermal stress study conducted on the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were

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subjected to two autoclave cycles. Tests were performed to determine the effects of thermal stress on the ketamine HCL injection product, the results of which are shown in tables 22 and 23.

[00034] Fig. 4 shows the manufacturing steps for the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure.

[00035] Fig. 5 shows the results of process sampling and analysis of bulk solution for three batches of the ketamine solution of the disclosure at 1 mg/mL.

[00036] Fig. 6 shows the results of process sampling and analysis of bulk solution for 3 batches of the ketamine solution of the disclosure at 2 mg/mL.

[00037] Fig. 7 shows the results of a filter compatibility and filling study for 4 batches of the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution at two different concentrations. Batches 1 and 2 are at 1 mg/mL of ketamine and batches 4 and 5 are at 2 mg/mL of ketamine.

[00038] Fig. 8 shows a diagram of a twist off closure that may be used with a sterile infusion bag comprising an aqueous ketamine solution of the disclosure.

DETAILED DESCRIPTION

[00039] The present invention includes ketamine prepared in a premixed, ready to use, formulation that does not require reconstitution or dilution prior to administration to a patient. In one aspect, the ketamine product of the disclosure is terminally sterilized in an infusion container with high integrity, and remains stable and active after prolonged storage. In another aspect, the ketamine product of the disclosure is produced under aseptic conditions. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated ketamine formulation prior to administration to a patient. The present invention includes ready-to-use ketamine formulations that do not comprise a preservative, or that do not contain an antimicrobial such as benzethonium chloride, but remain sterile and stable when stored at room temperature for a prolonged period (e.g., 24 months) in a sterile infusion container.

[00040] The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an infusion container. The premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, and remain active after prolonged storage.

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[00041] In one aspect, the present invention of the disclosure is a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection.

[00042] In certain aspects, the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

[00043] In certain aspects, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution is about 3.5 to 5.5.

[00044] In certain aspects, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, a complexing agent and a preservative. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

[00045] In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution without benzethonium chloride is formulated as a total volume of about 50- 500 mL.

[00046] In one aspect, the primary packaging for the ready-to-use, sterile aqueous ketamine solution without benzethonium chloride is an intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

[00047] In one aspect, the intravenous bag is made up of multilayer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer.

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Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

[00048] In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is an infusion container. In certain aspects, the infusion container is a flexible infusion bag. In certain aspects, the infusion bag comprises at least one port. In certain aspects, the infusion container is a prefilled syringe. In certain aspects, the infusion container is a glass container. In certain aspects, the infusion container is a semi-flexible plastic infusion container.

[00049] In one aspect, the ready to use, sterile infusion bag, comprising an aqueous ketamine solution without benzethonium chloride comprises at least one port. In some aspects, the port is a tube port closed with a closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer at least one port is a tube port. In certain aspects, the tube port comprises one or more layers of a plastic material.

[00050] In some aspects, the tube port comprises a PP/EVA material. In some aspects, the tube port comprises a multi-layer co-extruded connector tubing. In some aspects, the tube port is PVC-free and/or plasticizer free. In some aspects, the tubing port is sealed closed. Other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the port.

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[00051] In certain aspects the closure is a twist-off closure. In certain aspects, the closure comprises a membrane that creates a barrier, splitting the closure in two parts. In certain aspects, the closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, the closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the closure.

[00052] In certain aspects, the port may have a stopper, such as a rubber stopper, to provide a fluid tight closure of the passage and a lid member that clamps the periphery of the stopper. In certain aspects, the port may have a stopper comprising a plastic material. In a non-limiting embodiment, the port may have a resalable stopper which provides fluid tight closure of the passage and a plastic cap that clamps the periphery of the resealable stopper. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In a non-limiting embodiment, the port may be a resealable twist off port, which may also be referred to as a "spike port." In some embodiments, the infusion container of the present invention may optionally be overwrapped by an overwrap pouch covering the filled and sealed infusion container. In some embodiments, the infusion container is overwrapped by an aluminum pouch, which may further comprise other materials or a combination of other materials, for example, a four layer overwrap. The present invention does not relate to semi-solid topical formulations (such as gel, hydrogel, emulgel, paste, cream, ointment etc.), inhalations or aerosols and/or non-aqueous formulations that are not suitable for parenteral administration.

[00053] In one aspect, the infusion bag comprises a flexible film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof, etc. In certain aspects, the

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infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation; an M315 film manufactured by SealedAir Corporation; an APP-series film manufactured by Polycine, such as APP-114S film manufactured by Polycine; a polypropylene film, such as those manufactured by Technoflex, such as an Inerta® film manufactured by Technoflex; a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa; an Inerta 103 film, made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer, which may be manufactured by Technoflex; or another commercially-available polymer film designed for use in intravenous bag products. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the infusion bag.

[00054] In certain aspects, the infusion container (e.g., infusion bag) is contained in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

[00055] Aseptic processing involves sterile filtration and aseptic processing of a pharmaceutical product, wherein a premixed pharmaceutical solution is sterilized, for example, by filtering a pharmaceutical solution through a pre-filter with a filter absolute rating: 0.45 μm followed by a filtration through two sterilizing filters (0.2 μm pore size filters) under aseptic conditions, or similar conditions. The filtration can be pressure driven (conducted under compressed air). Aseptic filling of the sterile solution into a sterile container can be achieved, for

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example, by filling the pre-sterilized bag in line with filtration under aseptic conditions. After filling, port of the infusion bags used for product solution filling can be sealed.

[00056] Terminal sterilization involves sterilizing a pharmaceutical product in its sealed final container (e.g., in an infusion bag). A sterilizing agent or process is used to kill microbes and other pathogens to create a sterile final product. Terminal sterilization of ketamine formulations in infusion bags can be achieved by steam sterilization, heat sterilization, such as an autoclave method or any other methods known in the art; by radiation treatment such as Gamma, E-beam or ultraviolet; or by chemical sterilization, e.g., ethylene oxide. *See*, *e.g.*, U.S. Pat. No. 5,439,643 and 8,617,467, each incorporated herein by reference in their entireties. Heat sterilization may include steam sterilization and autoclaving. A terminally sterilized drug product undergoes final sterilization in a sealed container, and thus, enhances safety by reducing the risk of contamination. Terminal sterilization is one of the most difficult requirements for medical devices. It eliminates viable pathogens (e.g., microbes and viruses) to produce a sterile final product, but it involves conditions that can affect the integrity of the packaging, cause leaching of packaging components into the pharmaceutical solution, cause degradation of the drug product, and/or otherwise affect the stability the pharmaceutical solution. Every component of an infusion bag that is subjected to terminal sterilization (including the bag film, ports, and closures) must be able to withstand terminal sterilization conditions and must be compatible with the pharmaceutical solution components under those conditions.

[00057] In certain aspects, the terminal sterilization procedure of the ready to use terminally sterilized infusion container comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is autoclaving. Autoclaving involves application of elevated temperature and/or pressure to achieve sterilization. Other methods of terminal sterilization (e.g., ethylene oxide, radiation) also involve harsh conditions. Subjecting a pharmaceutical composition in a final container to terminal sterilization can adversely affect the pharmaceutical composition, the material of the final container, and the sealing integrity of the final container. Thus, not all pharmaceutical compositions and final containers are mutually suitable for terminal sterilization using heat sterilization. Heat sterilization may be performed using steam, preferably wet steam, or superheated water. The time period for the sterilization must be long enough to meet the sterility requirements required of an injectable product. When steam is used the period may be from about 5 to 30 minutes at temperatures of about 110° C to 130° C, or from about 10 to 30 minutes at

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temperatures of about 110° C to 130° C, preferably at 120° C to 125° C for 15 to 30 minutes. In another aspect, the sterilization can be at 120° C for 15 to 20 minutes. The pharmaceutical formulation should be analyzed after sterilization for the presence of leachables and other impurities.

[00058] In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15–30°C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, terminally sterilized, infusion container. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, sterile, infusion container.

[00059] In certain aspects, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure units tested does not exceed 6000 per container when the sterile infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 µm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 23, e.g., 0 to 23, 0 to 15, 0 to 10, 0 to 5, 0 to 4, 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 10 microns in size. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 3, e.g., 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 25 microns in size.

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[00060] In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are less than or equal to 1%. In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are not more than 2%, not more than 1.5%, not more than 1%, not more than 0.5%, not more than 0.2%, not more than 0.15%, or not more than 0.05%.

[00061] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 98.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 98%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97%.

[00062] In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, for example, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

[00063] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine without benzethonium chloride solution of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure

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after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.9% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution of the disclosure after long-term storage for months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00064] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00065] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or

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greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00066] In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (v); (vi) overwrapping the terminally sterilized infusion bag of step (v) with an overwrap. In certain aspects, the terminal sterilization is autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for about 15 minutes. In certain aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat insures a hermetic seal between the tube port and the film and tube port and closure.

[00067] In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution using the ready-to-use, sterile infusion bag to the subject; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

[00068] In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

[00069] In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

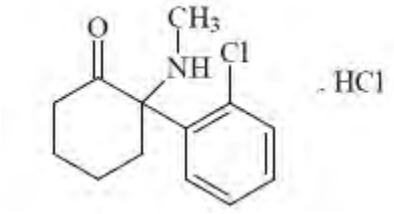
Definitions

[00070] The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the

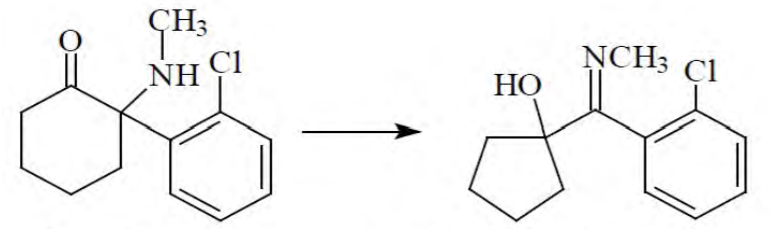
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practitioner in describing the compositions and methods of the present disclosure and how to make and use them.

[00071] As used herein, the term "ketamine" refers to (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone as the free base or in the form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of ketamine can include inorganic acid salts such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. In certain aspects, the ketamine salt is ketamine HCl. In other non-limiting embodiments, ketamine comprises the structure depicted below in Formula I:



[00072] Ketamine in aqueous solution has been shown to react under accelerated conditions of high temperature and pH by a process which involves initial formation of 1-[(2-chlorophenyl) (15ethylamino) methyl] cyclopentanol ("Compound A"). Thus, the term "Compound A" or "Impurity A" as used herein comprises the structure on the right-hand side of the reaction depicted below:



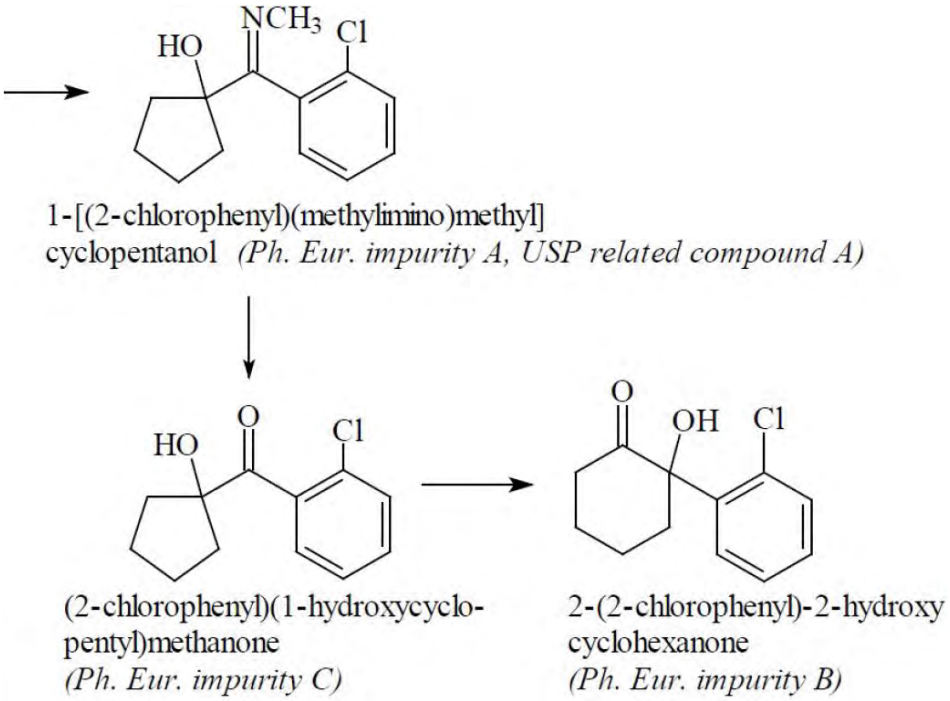
Ketamine

1-[(2-chlorophenyl)(methylimino)methyl] cyclopentanol *(Ph. Eur. impurity A, USP related compound A)*

[00073] Compound A, depending on temperature and pH, may then isomerize back to Ketamine or hydrolyze to the primary product of this reaction: (2-chlorophenyl)(1-hydroxycyclopentyl) methanone 2-(2-chlorophenyl)-2-hydroxycyclohexanone ("Impurity B") which may be major, although not primary product, that results from isomerization of (2-

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chlorophenyl)(1-hydroxycyclopentyl)methanone ("Impurity C"). The structures of "Compound A" (also referred to as "Impurity A"), "Impurity B," and "Impurity C," are depicted in the reaction below:



[00074] The term, "chemically stable," as used herein, refers to a chemical compound which retains its chemical structure and useful properties on a timescale of its expected usefulness. Specifically, the usefulness of the compound is maintained in the environment in which it is stored. Conversely, a compound lacks chemical stability if it decomposes under the conditions of a specific environment. As used herein in certain embodiments, "chemically stable" may mean resistant to degradation of ketamine into its known or unknown decomposition elements. The level of ketamine identified impurity that is acceptable can be up to 0.15% of the formulation as per the ICH guidelines for shelf-life determination, but in certain preferred embodiments, the amount of impurities is lower, *e.g.*, less than 0.05% of the formulation.

[00075] As used herein, the terms "premix", "premixed", or "premixture" refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of ketamine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

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[00076] As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

[00077] As used herein, the term "container closure system" refer to the sum of packaging components that together contain and protect the dosage form, including primary packaging components and secondary packaging components.

[00078] As used herein, the terms "primary packaging components," "primary packaging" means packaging components that are or may be in direct contact with the dosage form. For example, the primary packaging may be an infusion bag, including a flexible film component, one or more ports, and a closure system.

[00079] The terms "infusion bag," "intravenous bag," and "IV bag" may be used interchangeably herein and refer to a type of primary packaging, which comprises a bag film, port(s) and closure system(s). Such infusion bags may be used to administer intravenous infusion products.

[00080] The term "infusion container" as used herein refers to a type of primary packaging used to administer intravenous infusion products, for example, a flexible infusion bag, a semi-flexible plastic infusion container, a prefilled syringe, etc.

[00081] As used herein, the term "flexible" refers to a material that has the ability to deform and return to its original shape when the applied stress is removed without breaking or damage at around standard temperature and pressure (STP), for example about 0 °C ± 40 °C and 1 atm ± 0.005 atm. Flexible materials are distinguished from rigid materials such as glass. A "flexible" infusion bag allows fluid to drain out of the bag without venting. A "flexible" infusion bag may have port tubes and/or closures that are made of rigid or semi-rigid materials, provided that the bag film is flexible.

[00082] As used herein, the terms "secondary packaging components" and "overwrap" refer to a packaging component that is intended to provide additional protection to the drug product but is not typically in direct contact with the dosage form during storage.

[00083] As used herein, the terms "subject" or "patient" refer to a human, a non-human mammal or a non-human animal. The compounds and compositions of the present disclosure have

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application in veterinary medicine as well as for humans, e.g., for the treatment of domesticated species such as canine, feline, and various other pets; farm animal species such as bovine, equine, ovine, caprine, porcine, etc.; wild animals, e.g., in the wild or in a zoological garden; and avian species, such as chickens, turkeys, quail, songbirds, etc.

[00084] As used herein, the terms "pharmaceutical composition" or "pharmaceutical formulation" relates to compositions that can be formulated in any conventional manner using one or more pharmaceutically acceptable diluents or excipients. A "pharmaceutically acceptable" solvent, diluent or excipient, as used herein, means approved by a regulatory agency of the federal or a state government, or as listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans. Suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions).

[00085] As used herein, the terms "therapeutically effective dose," "dose," "effective amount," and "therapeutically effective amount" refer to an amount sufficient to produce the desired effect, which can be readily determined according to standard good medical practice by those of skill in the art. In other non-limiting embodiments, a therapeutically effective dose or effective amount may be any amount that produces a response that a user (e.g., a clinician) will recognize as an effective response to the therapy. Thus, a therapeutically effective amount will generally be an amount that induces a desired effect, such as, for example, sedation or analgesia.

[00086] As used herein, the terms "about" and "approximately" mean +/−20% of the recited value, or within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system.

[00087] As used herein, the terms "intensive care unit" or "ICU" refer to any setting that provides intensive care.

[00088] As used herein, the terms "port," "tubing port," or "port tube" refer to a connector which is sealed into the container portion of an infusion bag. An infusion bag may include one or more ports. The ports may include administrative and/or additive ports. The ports of the invention use commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization. The ports may be coextruded.

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[00089] As used herein, the term "closure" refers to a component that closes or seals a container. A closure provides an effective barrier against microbial contamination. In some aspects, the closure is a twist off closure. The closures referred to herein may comprise commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization.

[00090] As used herein, singular forms, including the singular forms "a" "an" and "the", specifically also encompass the plural referents of the terms to which they refer unless the context clearly dictates otherwise. In addition, as used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

[00091] As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

Pharmaceutical Formulations

[00092] The compounds and compositions of the invention may be formulated as pharmaceutical compositions by admixture with pharmaceutically acceptable solvents and excipients. For example, suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions). In certain non-limiting embodiments, the compounds or compositions are provided in a therapeutically effective amount to an animal, such as a mammal, preferably a human, in need of treatment therewith for inducing a sedative, anxiolytic, analgesic, or anesthetic effect.

[00093] In certain non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is the only therapeutically active ingredient present in the composition. In another non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is formulated in combination with at least one or more other

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therapeutically active ingredient. The formulation is suitable for parenteral administration, such as intravenous administration.

[00094] The pharmaceutical formulations suitable for injectable use, such as, for example, intravenous administration, include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. Solvents or dispersion mediums suitable for stable pharmaceutical formulations include, for example, water for injection (WFI), saline, aqueous dextrose, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and oils. In certain aspects, the solvent may be sterile WFI, 0.9% sodium chloride injection (normal saline), or 5% dextrose in water. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like. Exposure to potential microorganisms such as bacteria, viruses, and fungi can also be prevented using terminal sterilization of prefilled parenteral pharmaceutical products and packages or aseptic processing throughout the manufacturing process of the ketamine product.

[00095] Pharmaceutical formulations may include isotonicity adjusting agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions may be prepared by incorporating the ketamine in the required amounts in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtering and/or terminal sterilization.

[00096] Pharmaceutical formulations may include one or more excipients. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer; amino acids; urea; alcohols; ascorbic acid; phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrrolidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine; lipids; preservatives; suspending agents; stabilizers; and dyes. The term “stabilizer” refers to a compound optionally used in the pharmaceutical compositions of the present invention in order to increase storage life. Non-limiting examples of stabilizers include

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antioxidants. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers.

[00097] Pharmaceutical formulations may include a non-ionic surfactant. Preferred non-ionic surfactants include Polysorbate 20, Polysorbate 80, Triton X-100, Triton X-114, Nonidet P-40, Octyl α-glucoside, Octyl β-glucoside, Brij 35, Pluronic, and Tween 20.

Methods of Using Ready to Use Ketamine Compositions

[00098] As noted above, the methods of treatment of the invention are directed to methods of analgesia in a patient in need thereof comprising administration of ketamine to the patient, wherein the ketamine is administered in an amount effective to produce the desired effect.

[00099] The ketamine for use in the invention can be administered via any suitable route. In a non-limiting embodiment, the therapeutic compound can be delivered in a controlled or sustained release system. For example, a compound or composition may be administered using intravenous infusion, continuous infusion, or other modes of administration. In certain non-limiting embodiments, the dosage of ketamine can be individualized and titrated to the desired clinical effect.

[000100] The present disclosure includes the following non-limiting list of items:

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is free of benzethonium chloride, and wherein the ketamine product is sterile and ready-to-use (RTU).
2. The ketamine product of item 1, wherein the ketamine product has been terminally sterilized.
3. The ketamine product of any preceding item, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. The ketamine product of any preceding item, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.
5. The ketamine product of any preceding item, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerine, mannitol, potassium chloride, or any combination thereof.

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6. The ketamine product of any preceding item, wherein the aqueous ketamine solution comprises 0.9% sodium chloride.
7. The ketamine product of any preceding item, further comprising a pH adjusting agent.
8. The ketamine product of item 7 wherein the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof.
9. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3 to 6.
10. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3.5 to 5.5.
11. The ketamine product of any preceding item, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
12. The ketamine product of any preceding item, wherein the solution comprises one or more of a chelating agent, an antioxidant, a stabilizer, or a complexing agent.
13. The ketamine product of any preceding item, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
14. The ketamine product of any preceding item, wherein aqueous ketamine solution is formulated as a total volume of about 50- 500 mL.
15. The ketamine product of any one of items 11-14, wherein the at least one port comprises a plastic material.
16. The ketamine product of item 15, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
17. The ketamine product of any one of items 11-16, wherein the closure comprises a plastic material.
18. The ketamine product of any one of items 11-17, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts.

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19. The ketamine product of item 18, wherein the twist-off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, and a superior part of the membrane in contact with a zone that forms an air chamber into the closure.

20. The ketamine product of any one of items 18 to 19, wherein the twist-off closure comprises at least one layer of polypropylene.

21. The ketamine product of any one of items 18 to 20, wherein the twist-off closure comprises at least one layer of polyethylene.

22. The ketamine product of any one of items 11-21, wherein the port comprises at least one layer of block copolymer.

23. The ketamine product of any one of items 11-22, wherein the port comprises more than one layer of a block copolymer.

24. The ketamine product of any one of items 11-23, wherein the port comprises more than one layer of a polyolefin block copolymer.

25. The ketamine product of any one of items 11-24, wherein the infusion bag comprises a flexible multilayer film.

26. The ketamine product of any one of items 11-25, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin, polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, or any combination thereof.

27. The ketamine product of any one of items 11-26, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer.

28. The ketamine product of any one of items 11-27, wherein the infusion bag comprises a flexible multilayer film comprising polypropylene styrene-block copolymer.

29. The ketamine product of any one of items 11-28, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

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30. The ketamine product of any one of items 11-29, wherein the infusion bag comprises a 3-layer film comprising polypropylene styrene-block copolymer.

31. The ketamine product of any one of items 11-30, wherein the infusion bag is contained within an overwrap.

32. The ketamine product of item 31, wherein the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof.

33. The ketamine product of any one of items 31 to 32, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

34. The ketamine product of any preceding item, wherein the ketamine product has been autoclaved.

35. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

36. The ketamine product of item 35, wherein the ketamine is at a concentration of about 1 to about 2 mg/mL.

37. The ketamine product of any preceding item, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature.

38. The ketamine product of item 37, wherein the controlled room temperature is 15–30°C.

39. The ketamine product of any preceding item, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

40. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months.

41. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 25 μm does not exceed 60 per container following storage of the ketamine product at room temperature for 24 months.

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42. The ketamine product of any preceding item, wherein the total impurities in the aqueous ketamine solution is less than or equal to 1%.

43. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%.

44. The ketamine product of any preceding item, wherein the bacterial endotoxin content is less than 0.4 EU/mg.

45. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater compared to the ketamine content before storage.

46. The ketamine product of any preceding item, containing about 250 mg ketamine hydrochloride.

47. The ketamine product of any preceding item, containing about 500 mg ketamine hydrochloride.

48. A method of preparing the ketamine product of any preceding item, comprising:

    i) adding ketamine or a pharmaceutically acceptable salt thereof to water;

    ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent;

    iii) filtering the solution of step (ii);

    iv) filling the solution of step (iii) into an infusion bag; and

    v) terminally sterilizing the infusion bag of step (iv).

49. The method of item 48 further comprising overwrapping the terminally sterilized infusion bag with an overwrap.

50. The method of any one of items 48-49, wherein the terminal sterilization comprises autoclaving the infusion bag.

51. The method of item 50, wherein said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes.

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52. The method of any one of items 50-51, wherein said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes.

53. The method of any one of items 50-52, wherein said autoclaving is at a temperature of 121° C for about 15 minutes.

54. The method of any one of items 50-53, wherein the method comprises overwrapping the infusion bag of step (iv) prior to terminally sterilizing the infusion bag.

55. A method of treating a subject in need of analgesia, comprising administering the ketamine product of any one of items 1-47 to the subject as a continuous infusion.

56. The method of item 55, wherein the ketamine solution is administered by intravenous infusion.

57. The method of item 55 or item 56, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.

58. The method of item 55 or item 56, wherein the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

59. The method of item 55 or item 56, wherein the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

60. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

EXAMPLES

[000101] The following examples are merely illustrative of the presently disclosed subject matter and they should not be considered as limiting the scope of the present disclosure in any way.

Example 1: Exemplary Formulations

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[000102] In one embodiment, the ketamine product comprises the composition of Table 1.

TABLE 1

Ketamine Hydrochloride in Sodium Chloride Injection 1 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine as Ketamine HCl	1 mg/mL 1.15 mg/mL	250 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000103] In another embodiment, the ketamine product may comprise the composition of Table 2.

TABLE 2

Ketamine Hydrochloride in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine as Ketamine HCl	2 mg/mL 2.3 mg/mL	500 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000104] In another embodiment, the ketamine product may comprise the composition of Table 3.

TABLE 3

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Ketamine in Sodium Chloride Injection 1 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine (free base)	1 mg/mL	250 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000105] In another embodiment, the ketamine product may comprise the composition of Table 4.

TABLE 4

Ketamine in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine (free base)	2 mg/mL	500 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000106] The inventors contemplate that additional ketamine products may be provided in different volumes with the same proportion of components as listed in Tables 1-4 above. Further, the inventors contemplate that other solvent systems may be substituted for the sodium chloride and water for injection. As one example, 5% dextrose in water for injection may be used in place of sodium chloride in water for injection in the formulations above. Further the inventors contemplate that any pharmaceutically acceptable salt of ketamine may be used in the formulations

Par Health Inc. Ex. 1002-0042

above, using the concentration of ketamine as the free base listed in Tables 3 and 4 above. The ketamine formulations above beneficially do not require an antimicrobial such as benzethonium chloride. The ketamine formulations above beneficially do not require any preservative. Nonetheless, the inventors contemplate that one or more excipients, such as a chelating or complexing agent or an antioxidant, may be added to the formulation without reducing the stability of the ready-to-use ketamine product described herein.

Example 2: Study of Stability Following Terminal Sterilization

[000107] Batches of the ketamine solution with the formulations described in Table 1 (1 mg/ml) and Table 2 (2mg/ml) were manufactured to study the effect of terminal sterilization by autoclaving on product behavior. The primary packaging for each formulation included an infusion bag comprising a flexible multilayer film comprising a 3-layer polypropylene styrene-block copolymer based film (APP114S film manufactured by Polycine); a tube port comprising a multilayer polyolefin and styrene block copolymer tube material (APP107 manufactured by Polycine); and a twist off closure composed of low density polyethylene (LDPE) and polypropylene (PP). The closure comprised a membrane that created a barrier, wherein the inferior part of the membrane was in direct contact with the ketamine solution, while the superior part was in contact with a zone that forms an air chamber into the closure. Autoclaving of the primary packaging filled with the preservative-free ketamine formulations of Table 1 (1 mg/ml) and Table 2 (2 mg/ml), respectively, was conducted at a target temperature T= 121°C± 1°C and time at F0=15 according to USP <1222>, which is incorporated fully herein.

[000108] The objective of this study was to evaluate the quality of ketamine formulation seven days after the product is exposed to terminal sterilization processes at 121°C at different F=0. Only slight, not significant, pH decrease was noted. There was no significant variation on assay (%) of ketamine from before to after sterilization.

TABLE 5: Assay and pH before vs after sterilization

Product	**Ketamine Formulation 1mg/ml**			**Ketamine Formulation 2mg/ml**		
Batch	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Average Assay pre-sterilization (% of Ketamine base)	100.6	101.5	100.9	100.1	101.7	100.0
Assay post-sterilization (FP) (% of labelled amount of Ketamine base)	100.5	101.7	100.6	100.6	101.7	100.5
Extractable volume (ml)	251	252	251	252	251	252

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Product	Ketamine Formulation 1mg/ml			Ketamine Formulation 2mg/ml		
Batch	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Assay post-sterilization (FP) (%of Ketamine base)	100.1	100.9	100.2	99.8	101.3	99.7
Assay % change post- VS pre-sterilization	**-0.5**	**-0.6**	**-0.7**	**-0.3**	**-0.4**	**-0.3**
pH pre-sterilization (end of filling)	5.2	4.8	5.2	4.9	4.8	5.2
pH post-sterilization (FP)	4.6	4.5	4.6	4.6	4.4	4.7
Change in pH (post VS pre-sterilization)	**-0.6**	**-0.3**	**-0.6**	**-0.3**	**-0.4**	**-0.5**

[000109] For the ketamine product with the formulation described in Table 1 (1 mg/ml) the maximum pH decrease after sterilization was equal to 0.6 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.5 pH units.

[000110] For the ketamine product of the disclosure with the formulation described in Table 2 (2mg/ml) the maximum pH decrease after sterilization was equal to 0.5 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.4 pH units.

[000111] The results of Tables 5 show that the ketamine product of the invention can be terminally sterilized using autoclaving at a target temperature T= 121°C± 1°C and time at F0=15 according to USP <1222> without affecting the quality of ketamine formulation.

Example 3: Stability Studies

[000112] The terminally sterilized infusion bags, as described in Example 2, comprising a preservative-free aqueous ketamine solution with the formulation described in Table 1 (1 mg/ml) or Table 2 (2 mg/ml) were compared to a commercially available concentrated ketamine solution product in multi-dose glass vials containing the preservative benzethonium chloride. The commercially available concentrated products were diluted with 0.9% sodium chloride in a glass volumetric flask to achieve a concentration of 1 mg/mL or 2 mg/mL of Ketamine. The results for the 1 mg/ml and 2 mg/ml products are shown in Tables 6 and 7, respectively.

TABLE 6: Accelerated Condition 40 ± 2°C / <25% RH – 6 months

Batch	**Commercial Product Batch 1 (1 mg / mL)**	**Commercial Product Batch 2 (1 mg / mL)**	**Ketamine Product of the Disclosure**	**Ketamine Product of the Disclosure**	**Ketamine Product of the Disclosure**

Par Health Inc. Ex. 1002-0044

Test			Batch 1 (1 mg / mL)	Batch 2 (1 mg / mL)	Batch 3 (1 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	101.2	101.4	100.5	101.7	100.6
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	5.0	5.0	4.7	4.5	4.8
Osmolality (mOsmol/kg)	291	286	296	298	296

TABLE 7: Accelerated Condition 40 ± 2°C / <25% RH- 6 months

Batch	Commercial Product Batch 1 (2 mg / mL)	Commercial Product Batch 2 (2 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

Par Health Inc. Ex. 1002-0045

Test			Batch 1 (2 mg / mL)	Batch 2 (2 mg / mL)	Batch 3 (2 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.2	100.7	100.4	101.5	100.4
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.6
Osmolality (mOsmol/kg)	297	288	304	305	304

TABLE 8: Long term Condition 25 ± 2°C / 40 ± 5 % RH – 12 months

Batch	Commercial Product Batch 1 (1 mg / mL)	Commercial Product Batch 2 (1 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

Par Health Inc. Ex. 1002-0046

Test			Batch 1 (1 mg / mL)	Batch 2 (1 mg / mL)	Batch 3 (1 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.9	102.1	100.5	101.9	100.7
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	0.05	0.06
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	0.05	0.06
pH (pH Units)	5.1	5.0	4.8	4.5	4.8
Osmolality (mOsmol/kg)	287	290	293	294	295

TABLE 9: Long term Condition 25 ± 2°C / 40 ± 5 % RH – 12 months

Batch	Commercial Product Batch 1 (2 mg / mL)	Commercial Product Batch 2 (2 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

Par Health Inc. Ex. 1002-0047

Test			Batch 1 (2 mg / mL)	Batch 2 (2 mg / mL)	Batch 3 (2 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.3	102.3	100.5	101.7	100.6
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.8
Osmolality (mOsmol/kg)	287	299	301	303	303

[000113] After 6 months of stability testing at 40°C, there was no observed variation in the pH and in the color of the ketamine products of the disclosure contained in ready-to-use, terminally sterilized, infusion bags. After 6 months at 40°C there was no observed reduction in Ketamine Hydrochloride Assay compared to T=0 sterilized. The total impurities of the preservative-free

Par Health Inc. Ex. 1002-0048

ketamine formulations of the disclosure, packaged in ready-to-use, terminally sterilized, infusion bags were comparable with the results obtained at T= 0.

[000114] The results of Tables 6-9 surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride under accelerated conditions and long-term storage. While the average pH of ketamine solution in infusion bags seen in the experiment was 4.5 - 4.8 pH units and the average pH of the commercially available product when diluted for use was 4.9 - 5.2, the ketamine solution in infusion bags remained stable. Additionally, osmolality of ketamine solution in infusion bags seen in the experiment was comparable to the commercially available product, and both were inside the physiological range (according to the USP <785>, which is incorporated fully herein, the osmolality of blood ranges between 285 and 310 mOsmol/kg) and therefore comparable in the context of this evaluation. No significant change was noted during the stability studies and no degradation was detected despite of a lack of any antimicrobial, stabilizer or preservative in the ketamine products of the present disclosure.

Example 4: Stress Studies

[000115] The ketamine product of the disclosure was analyzed to evaluate critical product characteristics /parameters under stressed conditions. Stress testing was intended to identify the likely degradation products, which further helped in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used.

[000116] An oxidative stress study was conducted in accordance with the procedure set out in Fig. 1. The results for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:1 are shown in Tables 10 and 11, respectively, where "Δ" refers to the difference between the test batch and the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:1 ratio. The oxidative degradation 1:1 reported data was collected 72 hours after addition of the hydrogen peroxide.

TABLE 10: Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:1 with H_2O_2

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Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (1 mg/ml)**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.74	4.58	- 0.16
Osmolality	270 - 330	mOsmol/Kg	296	295	- 1
Assay	95.0-105.0	%	100.0	99.6	- 0.4
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 0 0

TABLE 11: Oxidative degradation results of ketamine solution 500 mg/250 mL (2 mg/ml) in ratio 1:1 with H_2O_2

Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (2 mg/ml)**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	-

Par Health Inc. Ex. 1002-0050

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Appearance of solution - Clarity	Clear	-	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.60	4.56	- 0.04
Osmolality	270 - 330	mOsmol/Kg	299	308	+ 9
Assay	95.0-105.0	%	99.7	99.6	- 0.1
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 0 0

[000117] The results shown in Tables 10-11 demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed after 72 hours after the ketamine solution was treated with hydrogen peroxide in stoichiometric ratio 1:1.

[000118] The results of the oxidative stress for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:10 are shown in Tables 12 and 13, respectively, where "Δ" refers to the difference between the blank sample and Batch 1. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:10 ratio. The reported data was collected 48 hours after addition of the hydrogen peroxide.

TABLE 12: Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Assay	95.0-105.0	%	100.2	99.2	- 1.0

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Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity RT 5.3	NMT 0.20	%	< 0.05	0.13	+ 0.13
- Unspecified unidentified impurity RT 9.0	NMT 0.20	%	< 0.05	0.14	+ 0.14
- Total impurities	NMT 1.0	%	< 0.05	0.27	+ 0.27

TABLE 13: Oxidative degradation results of ketamine solution 500 mg/250 mL in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Assay	95.0-105.0	%	100.1	99.5	- 0.6
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity RT 5.3	NMT 0.20	%	< 0.05	0.08	0.08
- Unspecified unidentified impurity RT 9.0	NMT 0.20	%	< 0.05	0.08	0.08
- Total impurities	NMT 1.0	%	< 0.05	0.16	0.16

Par Health Inc. Ex. 1002-0052

[000119] The results shown in Tables 12-13 demonstrate that there was a slight increase in impurities in the ketamine solution after 48 hours after the ketamine solution was treated with hydrogen peroxide in ratio 1:10.

[000120] An acid/alkaline study was conducted in accordance with the procedure set out in Fig. 2. These results demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed through one month of observation (t=1M) compared to the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) at pH 4.7, while the "test batch" refers to the formulation at varying test pH.

TABLE 14: Degradation results of ketamine solution 250 mg/250 mL at pH 2.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	2.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	300	-
Assay	95.0-105.0	%	100.3	100.4	100.0	100.2	100.4
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

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Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Particulate matter: - ≥ 10 micron - ≥ 25 micron	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

TABLE 15: Degradation results of ketamine solution 250 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	3.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	294	-
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter:	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

Par Health Inc. Ex. 1002-0054

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
- ≥ 10 micron - ≥ 25 micron							

TABLE 16: Degradation results of ketamine solution 250 mg/250 mL at pH 5.5

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	3.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	294	-
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	N° part/mL	 0 0	-	-	 0 0	 0 0

Par Health Inc. Ex. 1002-0055

TABLE 17: Degradation results of ketamine solution 250 mg/250 mL at pH 6.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	6.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	295	-
Assay	95.0-105.0	%	100.23	100.3	100.3	100.4	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 18: Degradation results of ketamine solution 500 mg/250 mL at pH 2.5

Par Health Inc. Ex. 1002-0056

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	2.48	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	309	-
Assay	95.0-105.0	%	100.1	100.7	100.3	100.2	100.5
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 19: Degradation results of ketamine solution 500 mg/250 mL at pH 3.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-

Par Health Inc. Ex. 1002-0057

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	3.51	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	305	-
Assay	95.0-105.0	%	100.1	100.4	100.1	100.0	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 1 0

TABLE 20: Degradation results of ketamine solution 500 mg/250 mL at pH 5.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-

Par Health Inc. Ex. 1002-0058

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	5.51	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	303	-
Assay	95.0-105.0	%	100.1	100.2	100.2	100.2	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 21: Degradation results of ketamine solution 500 mg/250 mL at pH 6.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-

Par Health Inc. Ex. 1002-0059

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
pH	3.5 - 5.5	pH Units	4.63	-	-	6.50	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	304	-
Assay	95.0-105.0	%	100.1	100.0	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

[000121] A heat degradation study was performed on the ketamine solution in infusion bags in accordance to the procedure set out in Fig. 2. The primary packaging used was the same infusion bags described in Example 2. No significant degradation of the ketamine solution in primary packaging was observed after two terminal sterilization cycles. The pH dropped slightly after each sterilization but it remained within the specification limits. These results demonstrate that the ketamine product of the invention is stable after two sterilization cycles conducted at 121 °C for 15 minutes each, as no significant change is noted in assay or impurity profile.

TABLE 22: Thermal stress results of Ketamine HCl Injection 250 mg/250 mL

Par Health Inc. Ex. 1002-0060

Test	Specifications	Unit	Blank sample	Sterilization F015	Double sterilization F015	Δ
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.7	4.5	4.3	- 0.4
Osmolality	270 - 330	mOsmol/Kg	296	292	294	- 2
Assay	95.0-105.0	%	100.0	99.5	98.9	- 1.2
Impurities						
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	N° part/mL	 0 0	 0 0	 1 0	 + 1 0

TABLE 23: Thermal stress results of Ketamine HCl Injection 500 mg/250 mL

Par Health Inc. Ex. 1002-0061

Test	Specifications	Unit	Blank sample	Sterilization F015	Double sterilization F015	Δ
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.6	4.3	4.1	- 0.5
Osmolality	270 - 330	mOsmol/Kg	299	303	300	+ 1
Assay	95.0-105.0	%	99.7	99.4	99.0	- 0.7
Impurities						
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 1 0	 +1 0

Example 5: Manufacturing Process Development

[000122] The ketamine product of the disclosure is an aqueous solution and is terminally sterilized. The manufacturing process involved dissolution of ketamine HCl in water for injection and addition of sodium chloride to adjust for tonicity in accordance to the procedure set out in Fig. 4.

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[000123] Complete dissolution was verified by in process sampling and analysis of bulk solution before terminal sterilization as shown in Figs. 5 and 6 and Table 23.

TABLE 23: Test results of Dissolution

Test	Limits	Units	Dissolution Time	1 mg/mL (as in Table 1)			2 mg/mL (as in Table 2)		
				Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Appearance	Clear, colorless to slightly yellowish solution free from visible particles	n/a	5 min	comply	comply	comply	comply	comply	comply
			10 min	comply	comply	comply	comply	comply	comply
			15 min	comply	comply	comply	comply	comply	comply
pH	*	pH Units	5 min	5.0	4.8	5.3	5.1	4.8	5.2
			10 min	5.0	4.8	5.2	4.9	4.8	5.3
			15 min	5.0	4.7	5.2	5.0	4.8	5.2
Conductivity	14.3 – 15.3 (for information only)	mS/cm	5 min	15.3	15.3	15.3	15.1	15.1	15.0
			10 min	15.3	15.2	15.3	15.2	15.0	15.0
			15 min	15.3	15.2	15.3	14.7	15.0	14.9
Bulk solution Density	1.002 – 1.005 (for information only)	g/mL	5 min	n/a	n/a	n/a	n/a	n/a	n/a
			10 min	n/a	n/a	n/a	n/a	n/a	n/a
			15 min	1.004	1.004	1.004	1.004	1.004	1.004
Ketamine Assay	95.0 – 105.0	% of Ketamine base	5 min	101.9	101.6	100.9	100.7	102.0	100.0
			10 min	101.7	101.4	100.9	100.9	101.8	100.3
			15 min	101.8	101.4	100.9	100.6	102.3	100.1
Sodium Chloride Assay	146.0 – 162.0	mmol/L	5 min	156.9	153.7	154.9	155.9	155.8	154.5
			10 min	157.6	155.7	155.0	156.4	156.2	154.6
			15 min	157.2	156.3	154.6	155.5	156.1	154.7
Osmolality	270 – 330	mOsmol/kg	5 min	299	299	289	302	304	302
			10 min	301	293	293	302	305	302
			15 min	296	294	297	299	305	302

[000124] The ketamine bulk solution was formulated as in Table 1 (1mg/ml) and Table 2 (2mg/ml) then filtered through a pre-filter (3 μm pore size) followed by a filtration through one filter (0.2 μm pore size filters). The in-line filtration was pressure driven (conducted under

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compressed air) and the drug product was then filled into infusion bags through the tube port in line with filtration. Drug product solution compatibility with the filter and robustness of the filling process was confirmed as shown in Fig. 7.

TABLE 24: Filter Compatibility

Filling stop duration	Test	Limits	Units	1 mg/mL		2 mg/mL	
				Batch 1	Batch 2	Batch 4	Batch 5
1 Hour	pH (20÷25°C)	3.5 – 5.5	pH Units	5.3	4.7	4.9	4.8
				5.3	4.7	4.9	4.8
				5.3	4.7	4.9	4.8
	Ketamine Assay	95.0 – 105.0	% of ketamine base	100.7	101.5	99.9	101.3
				100.6	101.6	100.0	101.7
				100.2	101.6	100.2	101.6
2 Hours	pH (20÷25°C)	3.5 – 5.5	pH Units	5.3	4.8	4.9	4.9
				5.3	4.8	4.9	4.8
				5.1	4.8	4.9	4.8
	Ketamine Assay	95.0 – 105.0	% of ketamine base	100.4	101.5	100.1	101.6
				100.5	101.6	100.1	101.6
				100.3	101.4	100.1	101.5

[000125] After filling the infusion bag with the ketamine solution, the tube port was sealed using a twist-off closure. Terminal sterilization was then conducted using the autoclave process described in Example 2. The closure and tube port are thermally sealed due to the autoclave temperature.

[000126] These results demonstrate that the manufacturing process in accordance to the procedure shown in Fig. 4 is compatible with manufacturing the ketamine product of the invention as no significant change is noted in the characteristics of the ketamine solution (such as the ketamine assay, pH, etc.) during the dissolution and filtering steps.

[000127] It is to be understood that any particular aspect of the present disclosure that falls within the prior art may be excluded from any one or more of the claims. Since such aspects are

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deemed to be part of the whole of the present disclosure, any part of the whole disclosure may be excluded even if the exclusion is not set forth explicitly herein. Additionally, it is to be understood that while the present disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and alterations are within the scope of the following claims.

Par Health Inc. Ex. 1002-0065

CLAIMS

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine product is sterile and ready-to-use (RTU).
2. The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.
3. The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. The ketamine product of claim 1, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.
5. The ketamine product of claim 1, wherein the ketamine solution is free of benzethonium chloride.
6. The ketamine product of claim 1, wherein the aqueous ketamine solution has pH of about 3 to about 6.
7. The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
8. The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
9. The ketamine product of claim 7, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
10. The ketamine product of claim 7, wherein the closure comprises a plastic material.
11. The ketamine product of claim 7, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

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12. The ketamine product of claim 10, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

13. The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyolefin, polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

14. The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

15. The ketamine product of claim 7, wherein the infusion bag comprises a 3-layer film comprising polypropylene styrene-block copolymer.

16. The ketamine product of claim 7, wherein the infusion bag is contained within an overwrap.

17. The ketamine product of claim 16, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

18. The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

20. The ketamine product of claim 19, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

21. The ketamine product of claim 1, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

22. The ketamine product of claim 19, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

Par Health Inc. Ex. 1002-0067

23. The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

24. The ketamine product of claim 1, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months; and/or

the average number of particles equal to or greater than 25 μm does not exceed 600 per container following storage of the ketamine product at room temperature for 24 months.

25. The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater compared to the ketamine content before storage.

26. A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

27. The method of claim 26, wherein the step of terminally sterilizing comprises autoclaving the infusion bag at a temperature between about 110 to about 130° C for a period of time of about 7 to about 60 minutes.

28. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

Par Health Inc. Ex. 1002-0068

29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

30. The ketamine product of claim 29, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

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ABSTRACT

The invention relates to a sterile, ready-to-use, stable aqueous solution of ketamine suitable for direct intravenous infusion to a patient in need thereof, wherein the composition is disposed within a sealed infusion container as a premixture. The invention further relates to aqueous solutions of ketamine that are free of antimicrobials such as benzethonium chloride and are shelf-stable. The pharmaceutical compositions can be used, for example, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.

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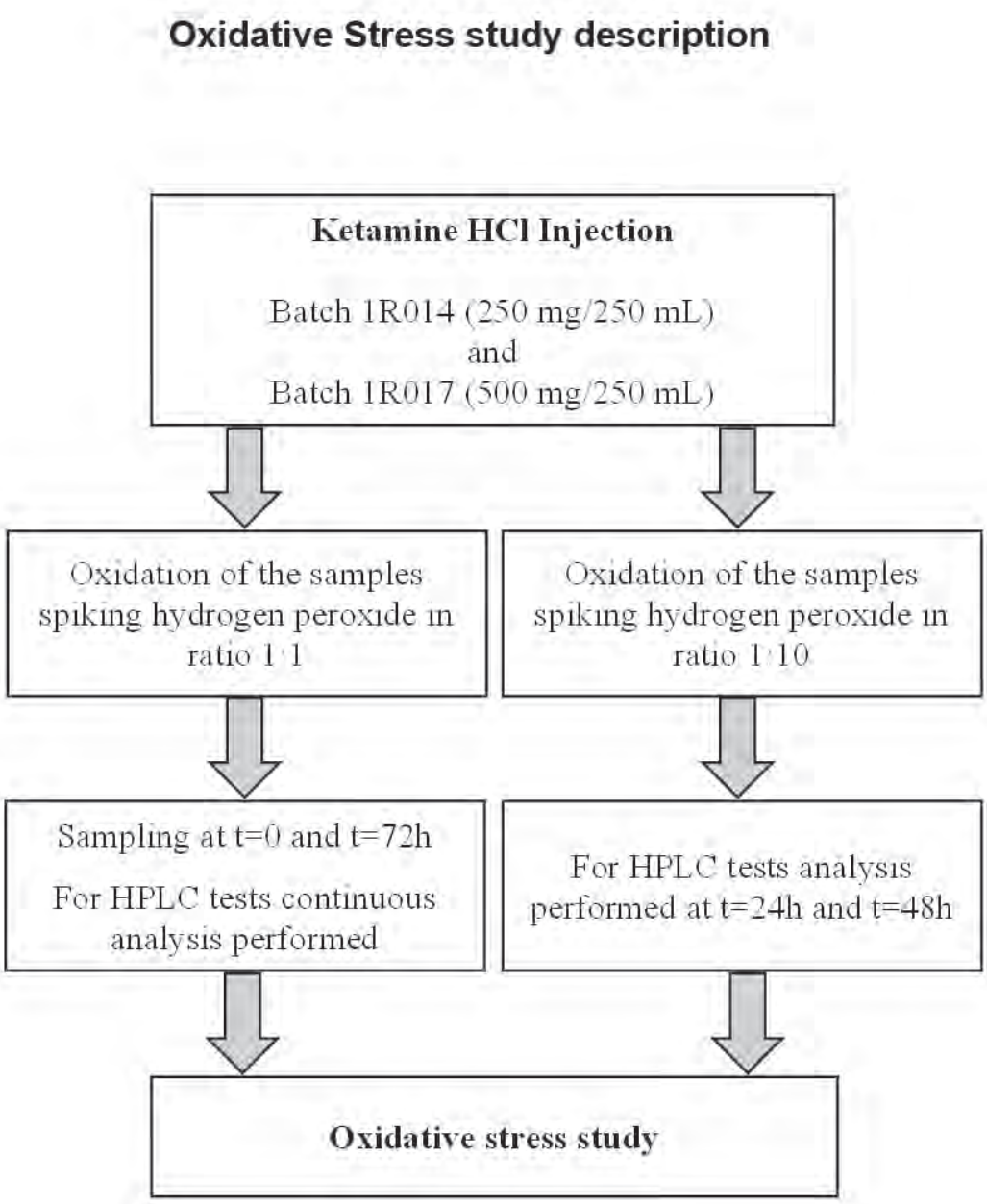

Oxidative Stress study description
Ketamine HCl Injection
Batch 1R014 (250 mg/250 mL)
and
Batch 1R017 (500 mg/250 mL)
Oxidation of the samples spiking hydrogen peroxide in ratio 1:1
Oxidation of the samples spiking hydrogen peroxide in ratio 1:10
Sampling at t=0 and t=72h
For HPLC tests continuous analysis performed
For HPLC tests analysis performed at t=24h and t=48h
Oxidative stress study

Fig. 1

Acid Alkaline stress study description

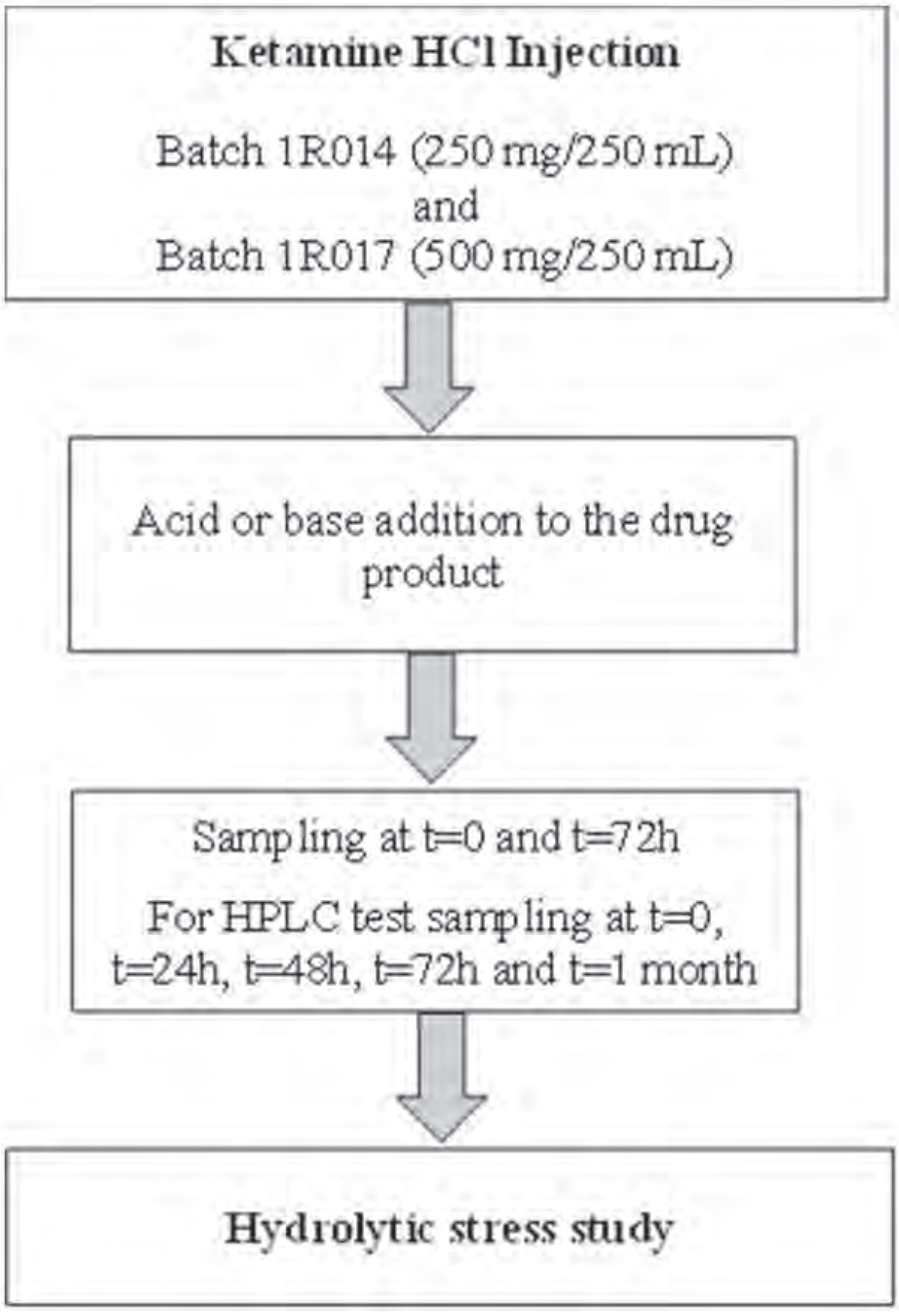


Fig. 2

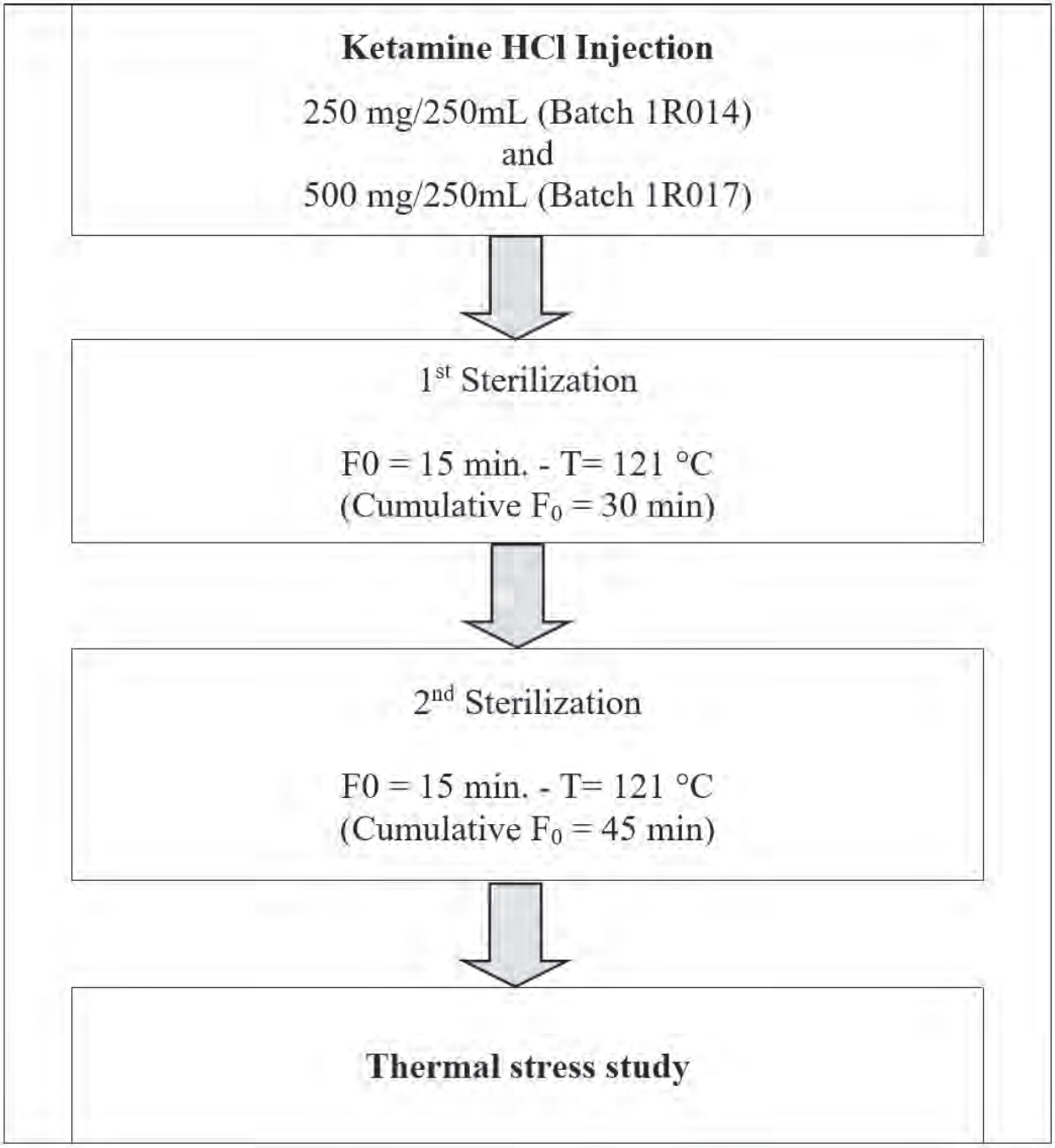

Ketamine HCl Injection
250 mg/250mL (Batch 1R014)
and
500 mg/250mL (Batch 1R017)
1st Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 30 min)
2nd Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 45 min)
Thermal stress study

Fig. 3

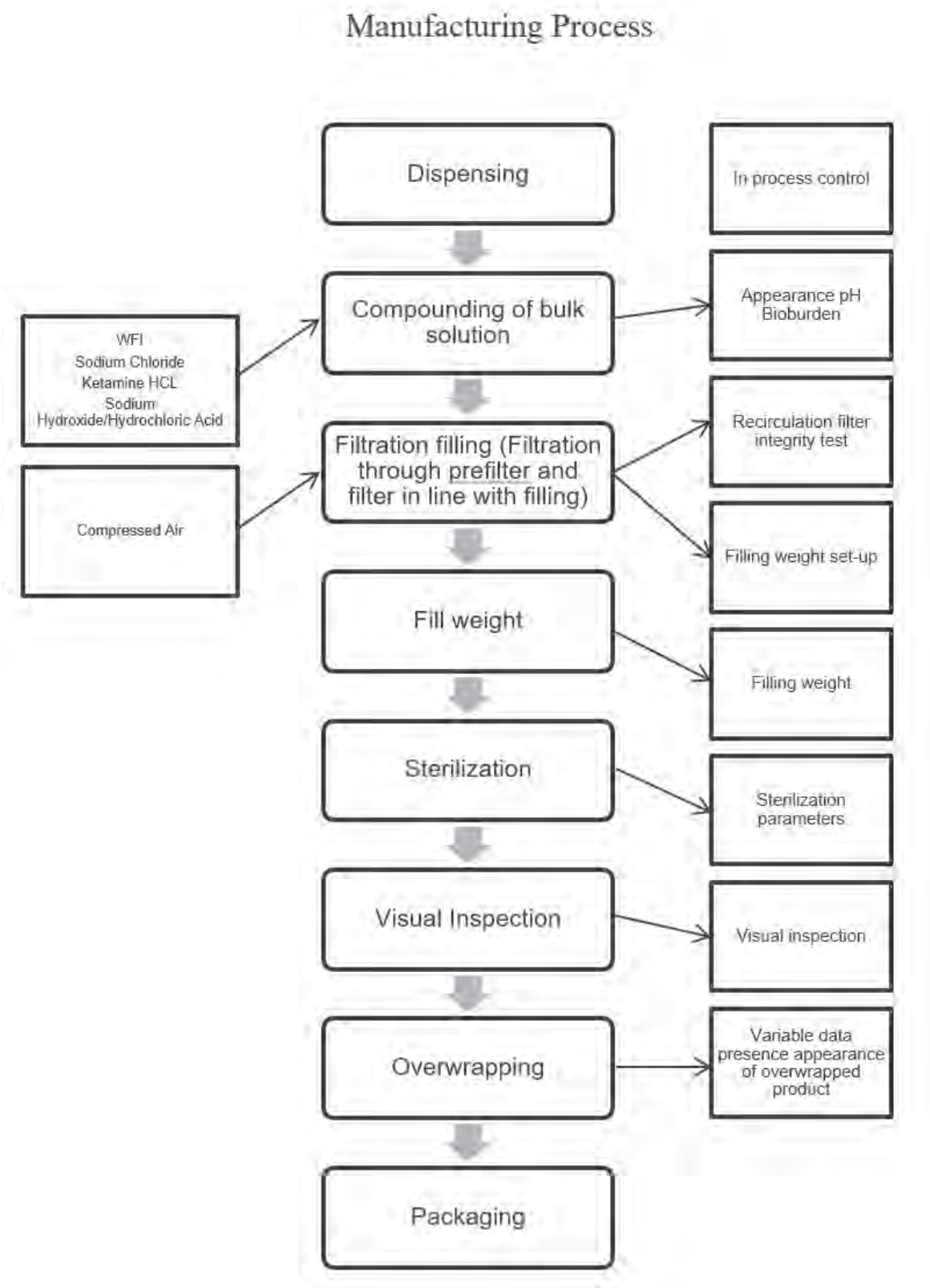

Manufacturing Process
Dispensing
In process control
Compounding of bulk solution
Appearance pH Bioburden
WFI
Sodium Chloride
Ketamine HCL
Sodium Hydroxide/Hydrochloric Acid
Filtration filling (Filtration through prefilter and filter in line with filling)
Recirculation filter integrity test
Compressed Air
Filling weight set-up
Fill weight
Filling weight
Sterilization
Sterilization parameters
Visual Inspection
Visual inspection
Overwrapping
Variable data presence appearance of overwrapped product
Packaging

Fig. 4

Graph 1: Ketamine Injection 1 mg/mL Dissolution Assay

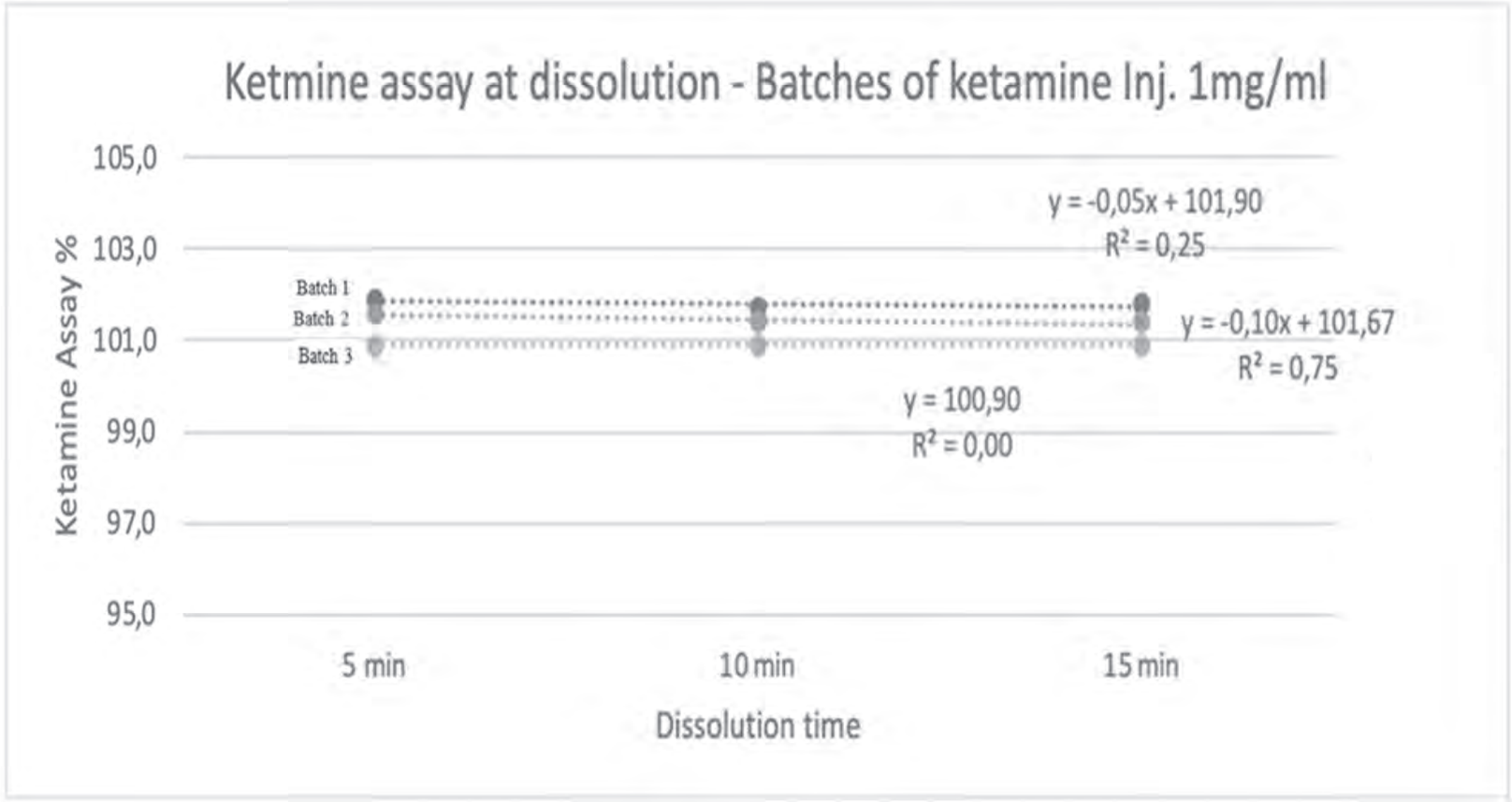


Fig. 5

Graph 2: Ketamine Injection 2 mg/mL Dissolution Assay

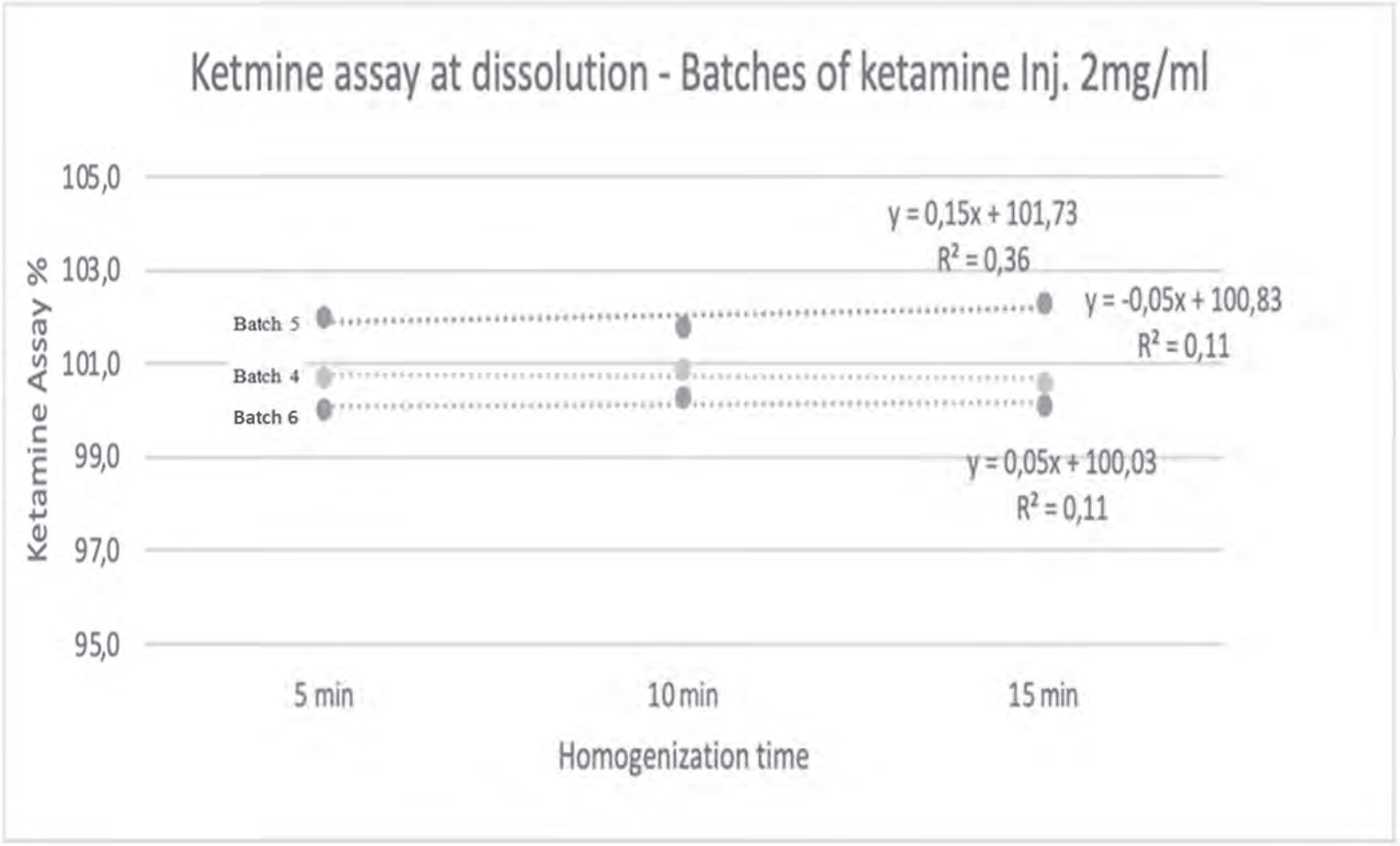


Fig. 6

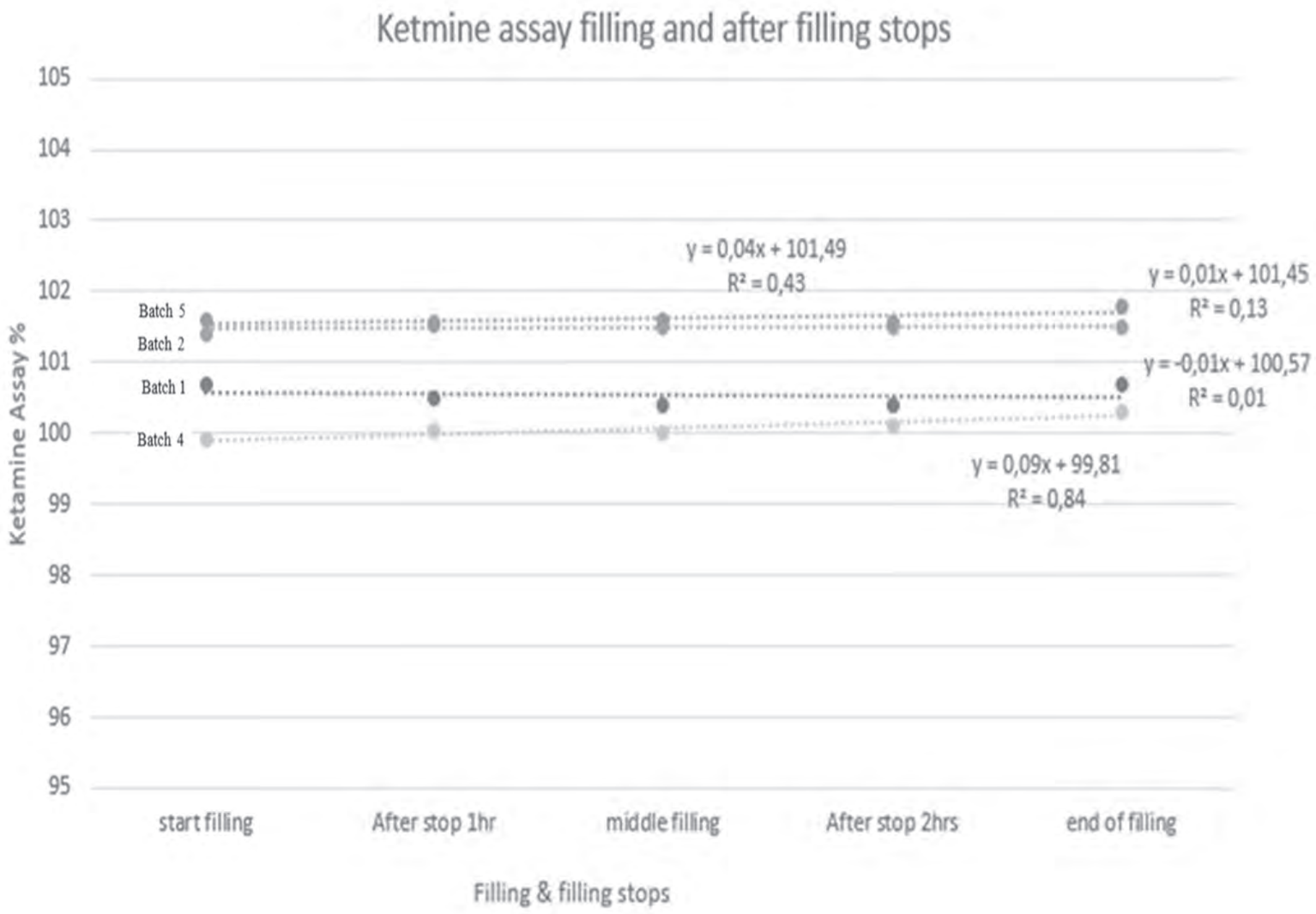

Ketmine assay filling and after filling stops
105
104
103
102
101
100
99
98
97
96
95
Ketamine Assay %
Batch 5
Batch 2
Batch 1
Batch 4
y = 0,04x + 101,49
R² = 0,43
y = 0,01x + 101,45
R² = 0,13
y = -0,01x + 100,57
R² = 0,01
y = 0,09x + 99,81
R² = 0,84
start filling
After stop 1hr
middle filling
After stop 2hrs
end of filling
Filling & filling stops

Fig. 7

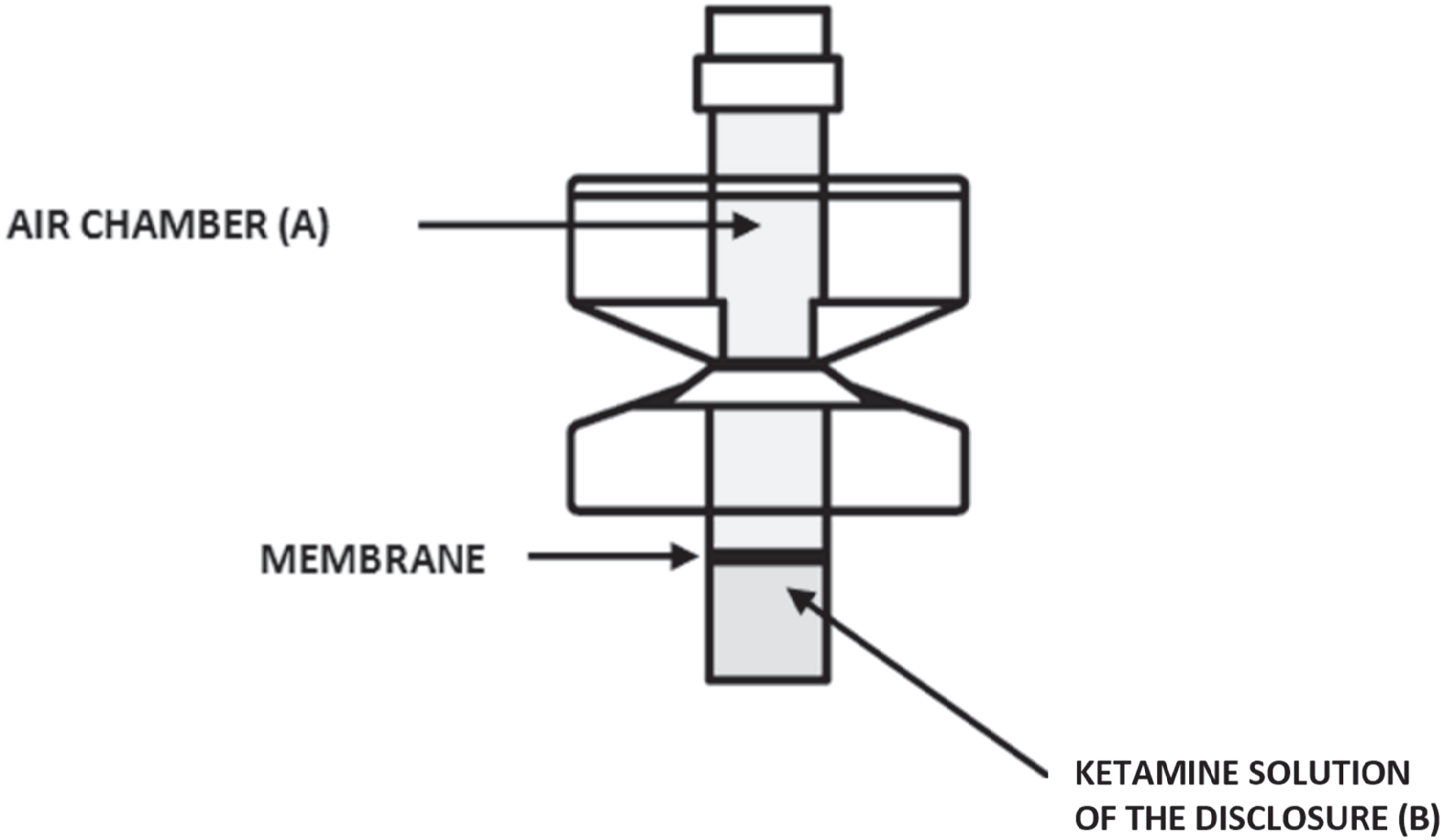

AIR CHAMBER (A)
MEMBRANE
KETAMINE SOLUTION
OF THE DISCLOSURE (B)

Fig. 8

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**07/11/2024 07:31:51 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	66329312	FILING DATE	-
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Aydin Harston

Documents

TOTAL DOCUMENTS: 13

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-114US2 ADS.pdf	8	Application Data Sheet	2174 KB
4830-114US2 Track One Request.pdf	2	Track One Request	185 KB
4830-114US2 DRAWINGS.pdf	8	Drawings-only black and white line drawings	1220 KB
4830-114US2 Declaration.pdf	1	Oath or Declaration filed	1050 KB
Ketamine Hydrochloride-Hospira-ANDA 074549-NPL.pdf	23	Non Patent Literature	1386 KB

Ketamine Hydrochloride-Hikma-ANDA 074524-NPL.pdf	20	Non Patent Literature	1318 KB
Ketamine Hydrochloride-AuroMedics-ANDA 076092-NPL.pdf	28	Non Patent Literature	1566 KB
Ketalar-NDA016812-NPL.pdf	13	Non Patent Literature	327 KB
4830-114US2 Ketamine TRACK ONE final clean FOR FILING-APP.TEXT.docx	60	Application body structured text document	611 KB

Warning: Bookmarks were found and have been removed.

785_ OSMOLALITY AND OSMOLARITY-NPL.pdf	3	Non Patent Literature	132 KB
4830-114US2 IDS.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1313 KB
1222_ Terminally Sterilized Pharmaceutical Products-NPL.pdf	7	Non Patent Literature	521 KB
4830-114US2 Ketamine TRACK ONE final clean FOR FILING.pdf	60	Auxiliary PDF of Application	793 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
4830-114US2 ADS.pdf	50652824A0C85F8D4127E7EEFF4F3C100C6D2BA04385234F74D50099E4E21E9AF001F981352CAC9F65323340ADF4367B157FBE56B335F564FB37AFE037293FD8

4830-114US2 Track One Request.pdf	2281407D4F5DEE3C1ECFCDBD25BD9B912AA3DBDA8E60078 18A6C447AA83D405055F97E5C3A2D93B8360D891B700808E6 DD5ED35B006B7290FB0754F5A093C3D4
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Ketamine Hydrochloride-Hospira-ANDA 074549-NPL.pdf	2CE27A9C9C87E97BCB154C1EC17E15E59CE0681DCB745D70 47D127EA0BBDA8C8F4D51A896D877CCF809D7FC5BF7D2F26 534C7553236F606A9579A6555E05F347
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4830-114US2 Ketamine TRACK ONE final clean FOR FILING-APP.TEXT.docx	84CAA5F1DE3BE862E0FD5DAC3F695743AA8FE43B43803BCA 4FFB6C6894CB4952A7623787B8A1C818FE314C114111006EA7 A4A04F5D21C53594EC7A4D6B4906D4
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4830-114US2 IDS.pdf	A65FF4DACB116CC4B9DEE88659E736A0A869C494F33C1309 DBD415FD57F174A49A274C4DAE48A146B2CF90FB5A68CA04 A8AD89E3B3F05D99EC3A486B6798D95F

1222_ Terminally Sterilized Pharmaceutical Products-NPL.pdf	FAA415A0C1912A872447324A4217148E88917C84AC57F88D59F9FDD3C1F2A3F06BAF83C6236EDACC1B335AC781EA81A03827B98BF36F75ED33FB0D415F37B03B
4830-114US2 Ketamine TRACK ONE final clean FOR FILING.pdf	14C94DD63880AE2131782150A62F0A7ADEC3F88A1306381F6103851A94296C3D5D742191FA2A056B909567580C522CC0979945FC551F56C7B0C74D22C10B72CA

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	07/11/2024 07:31:51 PM Z ET	4830-114US2

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

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PATENT CENTER #	66329312	AUTHORIZED BY	Aydin Harston
CUSTOMER #	6449	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Sergio DUSCI

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 022135	E20247AJ33008752	Charles Pace

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	140.00	1	140.00
1817	REQUEST FOR PRIORITIZED EXAMINATION	4200.00	1	4200.00
1111	UTILITY PATENT APPL. SEARCH FEE	700.00	1	700.00
1011	BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-ELECTRONIC FILING FEE UNDER 1.16(T))	320.00	1	320.00
1311	PATENT APPL. EXAMINATION FEE	800.00	1	800.00

1202	EACH CLAIM IN EXCESS OF 20	100.00	10	1000.00

TOTAL AMOUNT: **$7,160.00**

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PTO/SB/08a (01-22)
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(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Sergio DUSCI
Art Unit	
Examiner Name	
Attorney Docket Number	4830-114US2

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	1	5439643	A	1995-08-08	LIEBERT	
	2	8617467	B2	2013-12-31	RODRIGUEZ ET AL	

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Par Health Inc. Ex. 1002-0085

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	Application Number	
	Filing Date	
	First Named Inventor	Sergio DUSCI
	Art Unit	
	Examiner Name	
	Attorney Docket Number	4830-114US2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Ketamine Hydrochloride-ketamine hydrochloride injection, solution, concentrate, Hospira-ANDA 074549, 2022 (23 pages)	☐
	2	Ketamine Hydrochloride-ketamine hydrochloride injection, Hikma-ANDA 074524, 2022 (20 pages)	☐
	3	Ketamine Hydrochloride-ketamine hydrochloride injection, AuroMedics-ANDA 076092, 2022 (28 pages)	☐
	4	Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, 2022 (13 pages)	☐
	5	<785> OSMOLALITY AND OSMOLARITY, (http://www.uspbpep.com/usp31/v31261/usp31nf26s1_c785.asp), Pharmacopeial Forum : Volume No. 34(1), 2024 (3 pages)	☐
	6	<1222> Terminally Sterilized Pharmaceutical Products—Parametric Release, (https://www.uspnf.com/purchase-usp-nf#:~:text=The%20current%20version%20of%20USP,official%20on%20May%201%2C%202024), United States Pharmacopeia (2024). (7 pages)	☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Par Health Inc. Ex. 1002-0086

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Sergio DUSCI
	Art Unit	
	Examiner Name	
	Attorney Docket Number	4830-114US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Aydin H. Harston/	Date (YYYY-MM-DD)	2024-07-11
Name/Print	Aydin H. Harston, Ph.D.	Registration Number	65,249

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

READY-TO-USE KETAMINE PREMIX FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. provisional application number 63/513,225, filed July 12, 2023 the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to ready-to-use, sterile, premixed formulations of ketamine, or a pharmaceutically acceptable salt thereof, that does not include benzethonium chloride, is chemically stable for approximately 24 months or more, and can be used, for example, to treat a subject in need of anesthesia for a diagnostic or a surgical procedure.

BACKGROUND

[0003] Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride. Ketamine is a noncompetitive, high affinity NMDA receptor antagonist. Ketamine's mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system. Ketamine has been used as an anesthetic agent.

[0004] Most preparations of ketamine contain equal (1:1) concentrations of its two enantiomers: S (+) ketamine and R (−) ketamine. Ketamine formulations that are commercially available and approved by the FDA in the U.S. currently contain benzethonium chloride added as a preservative.

[0005] Ketamine can be administered to a patient in a variety of ways. For example, ketamine can be used as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Alternatively, ketamine can be administered for the induction of anesthesia prior to the administration of other general anesthetic agents or as a supplement to other anesthetic agents.

[0006] The container closure system of a product intended for parenteral use has to ensure continuous compliance with the storage and handling specifications throughout the product shelf life to maintain functionality and drug delivery accuracy. Several factors have to be considered when choosing the right container closure system for an injectable product, such as drug product formulation properties, dosage, type of application, stability, stability when subjected to extreme

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conditions (such as during terminal sterilization), sterility, container closure integrity, storage conditions and duration, and end-user friendliness. Thus, there is a need to develop container closure systems that are appropriate for specific injectable products that maintains functionality and drug delivery accuracy.

[0007] Vials are the most common primary packaging for administration of ketamine injectables on the market in the U.S. Such vials contain concentrated ketamine solution. For intravenous (IV) administration, it is necessary to introduce the ketamine solution into an infusion container containing a suitably diluted IV solution. Thus, to date, ketamine has been provided as a concentrate that must be diluted with sterile water for injection (WFI), a sodium chloride solution, saline, or a dextrose in water solution prior to administration to a patient and must be used immediately after dilution. If the entire vial is not required, then the vial must still be disposed of as the vials are single use only.

[0008] There is no available single intravenous dosage form that provides a sterile, ready-to–use, stable, liquid formulation of ketamine that can be administered without any manipulation to a patient in need thereof, thereby avoiding a compromise with the sterility, an error in dosing accuracy and/or in medicament preparation etc. There is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine which can be administered to a patient in need thereof without deviation or manipulations and while preserving the sterility of the product, and optionally with a provision for administering along with other medicaments for combination or sequential therapy, if needed or desired. There also is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine that does not contain a preservative or antimicrobial such as benzethonium chloride. Preferably the shelf-life of the sterile, ready to use ketamine solution will be 24 months or more at room temperature.

SUMMARY OF THE INVENTION

[0009] In the present invention, the inventors have overcome multiple problems of prior art ketamine formulations, such as additional costs and inconvenience; the risk of potential contamination due to inadvertent medical error; long-term storage of a ready to use dosage of a stable, preservative-free ketamine solution. The inventors have developed a sterile, stable liquid formulation of ketamine in an infusion container that is at a ready to use concentration. For plastic materials being considered for use as primary packing materials for the infusion container, the challenge has been to develop packaging that is compatible with the contents, minimizes

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extractables/leachables, are solvent-resistant, and are durable. The packaging of a pharmaceutical product should desirably be stable and mutually compatible under terminal sterilization conditions, as packaging materials and terminal sterilization can affect the condition of different formulations. A sterile ready to use ketamine formulation in an infusion container avoids the expense, inconvenience, delay, and risk of contamination, and provides significant advantages over currently available concentrated formulations. Additionally, the inventors have beneficially developed a formulation of ketamine that is shelf-stable in an infusion container for greater than three months, and preferably for 24 months or more, without the use of preservatives or antimicrobials such as benzethonium chloride.

[00010] The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an intravenous bag or other infusion container. The ready-to-use premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, e.g., in a ready-to-use infusion bag (also referred to as a "ready-to-use bag").

[00011] In one aspect, the ketamine product of the disclosure is a ready-to-use, sterile, infusion bag comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection. In one aspect, the ketamine product is terminally sterilized. In one aspect, the ketamine product comprise a sterile aqueous ketamine solution that is aseptically filled, for example, the sterile aqueous ketamine solution is filled under aseptic conditions into a sterile infusion bag. In one aspect, the ketamine product of the disclosure is free of a preservative or antimicrobial such as benzethonium chloride.

[00012] In one aspect, the ready-to-use, sterile, infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

[00013] In one aspect, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3.5 to 5.5.

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[00014] In one aspect, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, and a complexing agent. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

[00015] In one aspect, the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution is formulated as a total volume of about 50- 500 mL.

[00016] In one aspect, the ready-to-use, sterile, infusion bag comprising aqueous ketamine solution without benzethonium chloride comprises at least one port. In one aspect, the ready to use terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride comprises at least one tube port closed with a closure. In certain aspects, the closure is a twist off closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the twist off closure comprises a membrane that creates a barrier, splitting the twist-off closure in two parts. In certain aspects, the twist off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure as illustrated in Figure 8. In certain aspects, the twist off closure comprises at least one layer of polypropylene. In certain aspects, the closure is a rubber stopper. In certain aspects, the twist off closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises a plastic material. In certain aspects, the closure is a cap. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer. In certain aspects, the tube port comprises one or more layers of a plastic material.

[00017] In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible multilayer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, filling, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials

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such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof etc. In certain aspects, the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a flexible multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a flexible multilayer film in which certain layers are comprised of different polymers or polymer blends from other layers. In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible single layer film.

[00018] In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a flexible intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use terminally sterilized aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

[00019] In one aspect, the infusion container may be enclosed in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

[00020] In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized by autoclaving. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using steam sterilization. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using heat sterilization. In one aspect, the ready-to-use infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by radiation. In one aspect, the ready-to-use, infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by chemical sterilization (e.g., ethylene oxide).

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[00021] In one aspect, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than three months at room temperature. In some aspects, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than six months, greater than twelve months, greater than eighteen months, or greater than twenty-four months at room temperature. In one aspect, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15–30°C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, terminally sterilized, infusion container.

[00022] In one aspect, the average number of particles equal to or greater than 10 µm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 6000 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 µm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 µm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 µm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months.

[00023] In one aspect, the impurities in the ready-to-use, sterile, infusion bag comprising a aqueous ketamine solution without benzethonium chloride total not more than 1%, not more than 0.4%, not more than 0.3%, not more than 0.2%, not more than 0.15%, or not more than 0.05%, or not more than 0.01%.

[00024] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25%

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RH for 6 months is greater than 98%, greater than 99%, or greater than 99.5%, or greater than 99.9%, or greater than 99.95%.

[00025] In one aspect, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In one aspect, the bacterial endotoxin in the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

[00026] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater.

[00027] In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized, infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (iv); (vii) overwrapping the terminally sterilized infusion bag of step (vi) with an overwrap. In certain aspects, the terminal sterilization is conducted by autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for about 15 minutes. In certain

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aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat ensures a hermetic seal between the tube port and the film and the tube port and closure.

[00028] In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution from the ready-to-use, sterile infusion bag to the subject without diluting the ketamine solution; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

[00029] In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

[00030] In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[00031] Fig. 1 shows the steps and specifications of the oxidative stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine product of the disclosure"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were spiked with hydrogen peroxide at different ratios (1:1 and 1:10). HPLC tests were performed to determine the effects of oxidative stress on the ketamine HCL injection product.

[00032] Fig. 2 shows the steps and specifications of the acid alkaline stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). An acid or base was added to two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively). HPLC tests were performed to determine the effects of hydrolytic stress on the ketamine HCL injection product.

[00033] Fig. 3 shows the steps and specifications of the thermal stress study conducted on the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were

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subjected to two autoclave cycles. Tests were performed to determine the effects of thermal stress on the ketamine HCL injection product, the results of which are shown in tables 22 and 23.

[00034] Fig. 4 shows the manufacturing steps for the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure.

[00035] Fig. 5 shows the results of process sampling and analysis of bulk solution for three batches of the ketamine solution of the disclosure at 1 mg/mL.

[00036] Fig. 6 shows the results of process sampling and analysis of bulk solution for 3 batches of the ketamine solution of the disclosure at 2 mg/mL.

[00037] Fig. 7 shows the results of a filter compatibility and filling study for 4 batches of the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution at two different concentrations. Batches 1 and 2 are at 1 mg/mL of ketamine and batches 4 and 5 are at 2 mg/mL of ketamine.

[00038] Fig. 8 shows a diagram of a twist off closure that may be used with a sterile infusion bag comprising an aqueous ketamine solution of the disclosure.

DETAILED DESCRIPTION

[00039] The present invention includes ketamine prepared in a premixed, ready to use, formulation that does not require reconstitution or dilution prior to administration to a patient. In one aspect, the ketamine product of the disclosure is terminally sterilized in an infusion container with high integrity, and remains stable and active after prolonged storage. In another aspect, the ketamine product of the disclosure is produced under aseptic conditions. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated ketamine formulation prior to administration to a patient. The present invention includes ready-to-use ketamine formulations that do not comprise a preservative, or that do not contain an antimicrobial such as benzethonium chloride, but remain sterile and stable when stored at room temperature for a prolonged period (e.g., 24 months) in a sterile infusion container.

[00040] The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an infusion container. The premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, and remain active after prolonged storage.

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[00041] In one aspect, the present invention of the disclosure is a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection.

[00042] In certain aspects, the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

[00043] In certain aspects, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution is about 3.5 to 5.5.

[00044] In certain aspects, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, a complexing agent and a preservative. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

[00045] In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution without benzethonium chloride is formulated as a total volume of about 50- 500 mL.

[00046] In one aspect, the primary packaging for the ready-to-use, sterile aqueous ketamine solution without benzethonium chloride is an intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

[00047] In one aspect, the intravenous bag is made up of multilayer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer.

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Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

[00048] In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is an infusion container. In certain aspects, the infusion container is a flexible infusion bag. In certain aspects, the infusion bag comprises at least one port. In certain aspects, the infusion container is a prefilled syringe. In certain aspects, the infusion container is a glass container. In certain aspects, the infusion container is a semi-flexible plastic infusion container.

[00049] In one aspect, the ready to use, sterile infusion bag, comprising an aqueous ketamine solution without benzethonium chloride comprises at least one port. In some aspects, the port is a tube port closed with a closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer at least one port is a tube port. In certain aspects, the tube port comprises one or more layers of a plastic material.

[00050] In some aspects, the tube port comprises a PP/EVA material. In some aspects, the tube port comprises a multi-layer co-extruded connector tubing. In some aspects, the tube port is PVC-free and/or plasticizer free. In some aspects, the tubing port is sealed closed. Other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the port.

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[00051] In certain aspects the closure is a twist-off closure. In certain aspects, the closure comprises a membrane that creates a barrier, splitting the closure in two parts. In certain aspects, the closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, the closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the closure.

[00052] In certain aspects, the port may have a stopper, such as a rubber stopper, to provide a fluid tight closure of the passage and a lid member that clamps the periphery of the stopper. In certain aspects, the port may have a stopper comprising a plastic material. In a non-limiting embodiment, the port may have a resalable stopper which provides fluid tight closure of the passage and a plastic cap that clamps the periphery of the resealable stopper. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In a non-limiting embodiment, the port may be a resealable twist off port, which may also be referred to as a "spike port." In some embodiments, the infusion container of the present invention may optionally be overwrapped by an overwrap pouch covering the filled and sealed infusion container. In some embodiments, the infusion container is overwrapped by an aluminum pouch, which may further comprise other materials or a combination of other materials, for example, a four layer overwrap. The present invention does not relate to semi-solid topical formulations (such as gel, hydrogel, emulgel, paste, cream, ointment etc.), inhalations or aerosols and/or non-aqueous formulations that are not suitable for parenteral administration.

[00053] In one aspect, the infusion bag comprises a flexible film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof, etc. In certain aspects, the

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infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation; an M315 film manufactured by SealedAir Corporation; an APP-series film manufactured by Polycine, such as APP-114S film manufactured by Polycine; a polypropylene film, such as those manufactured by Technoflex, such as an Inerta® film manufactured by Technoflex; a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa; an Inerta 103 film, made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer, which may be manufactured by Technoflex; or another commercially-available polymer film designed for use in intravenous bag products. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the infusion bag.

[00054] In certain aspects, the infusion container (e.g., infusion bag) is contained in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

[00055] Aseptic processing involves sterile filtration and aseptic processing of a pharmaceutical product, wherein a premixed pharmaceutical solution is sterilized, for example, by filtering a pharmaceutical solution through a pre-filter with a filter absolute rating: 0.45 μm followed by a filtration through two sterilizing filters (0.2 μm pore size filters) under aseptic conditions, or similar conditions. The filtration can be pressure driven (conducted under compressed air). Aseptic filling of the sterile solution into a sterile container can be achieved, for

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example, by filling the pre-sterilized bag in line with filtration under aseptic conditions. After filling, port of the infusion bags used for product solution filling can be sealed.

[00056] Terminal sterilization involves sterilizing a pharmaceutical product in its sealed final container (e.g., in an infusion bag). A sterilizing agent or process is used to kill microbes and other pathogens to create a sterile final product. Terminal sterilization of ketamine formulations in infusion bags can be achieved by steam sterilization, heat sterilization, such as an autoclave method or any other methods known in the art; by radiation treatment such as Gamma, E-beam or ultraviolet; or by chemical sterilization, e.g., ethylene oxide. *See*, *e.g.*, U.S. Pat. No. 5,439,643 and 8,617,467, each incorporated herein by reference in their entireties. Heat sterilization may include steam sterilization and autoclaving. A terminally sterilized drug product undergoes final sterilization in a sealed container, and thus, enhances safety by reducing the risk of contamination. Terminal sterilization is one of the most difficult requirements for medical devices. It eliminates viable pathogens (e.g., microbes and viruses) to produce a sterile final product, but it involves conditions that can affect the integrity of the packaging, cause leaching of packaging components into the pharmaceutical solution, cause degradation of the drug product, and/or otherwise affect the stability the pharmaceutical solution. Every component of an infusion bag that is subjected to terminal sterilization (including the bag film, ports, and closures) must be able to withstand terminal sterilization conditions and must be compatible with the pharmaceutical solution components under those conditions.

[00057] In certain aspects, the terminal sterilization procedure of the ready to use terminally sterilized infusion container comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is autoclaving. Autoclaving involves application of elevated temperature and/or pressure to achieve sterilization. Other methods of terminal sterilization (e.g., ethylene oxide, radiation) also involve harsh conditions. Subjecting a pharmaceutical composition in a final container to terminal sterilization can adversely affect the pharmaceutical composition, the material of the final container, and the sealing integrity of the final container. Thus, not all pharmaceutical compositions and final containers are mutually suitable for terminal sterilization using heat sterilization. Heat sterilization may be performed using steam, preferably wet steam, or superheated water. The time period for the sterilization must be long enough to meet the sterility requirements required of an injectable product. When steam is used the period may be from about 5 to 30 minutes at temperatures of about 110° C to 130° C, or from about 10 to 30 minutes at

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temperatures of about 110° C to 130° C, preferably at 120° C to 125° C for 15 to 30 minutes. In another aspect, the sterilization can be at 120° C for 15 to 20 minutes. The pharmaceutical formulation should be analyzed after sterilization for the presence of leachables and other impurities.

[00058] In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15–30°C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, terminally sterilized, infusion container. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5% when stored in the ready-to-use, sterile, infusion container.

[00059] In certain aspects, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure units tested does not exceed 6000 per container when the sterile infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 µm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 µm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 23, e.g., 0 to 23, 0 to 15, 0 to 10, 0 to 5, 0 to 4, 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 10 microns in size. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 3, e.g., 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 25 microns in size.

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[00060] In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are less than or equal to 1%. In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are not more than 2%, not more than 1.5%, not more than 1%, not more than 0.5%, not more than 0.2%, not more than 0.15%, or not more than 0.05%.

[00061] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 98.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 98%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97%.

[00062] In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, for example, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

[00063] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine without benzethonium chloride solution of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure

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after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99.9% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution of the disclosure after long-term storage for months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00064] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00065] In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 97.5% or

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greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater.

[00066] In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (v); (vi) overwrapping the terminally sterilized infusion bag of step (v) with an overwrap. In certain aspects, the terminal sterilization is autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C for about 15 minutes. In certain aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat insures a hermetic seal between the tube port and the film and tube port and closure.

[00067] In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution using the ready-to-use, sterile infusion bag to the subject; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

[00068] In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

[00069] In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

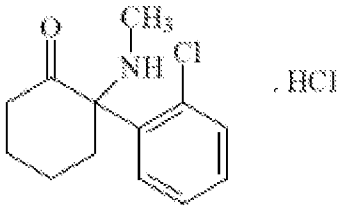
Definitions

[00070] The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the

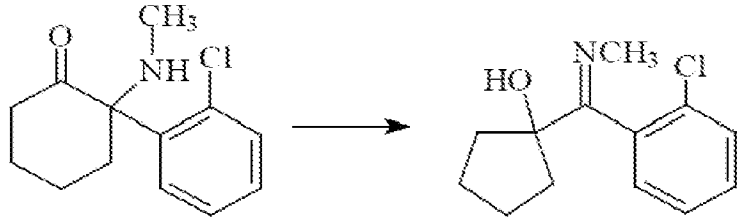
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practitioner in describing the compositions and methods of the present disclosure and how to make and use them.

[00071] As used herein, the term "ketamine" refers to (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone as the free base or in the form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of ketamine can include inorganic acid salts such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. In certain aspects, the ketamine salt is ketamine HCl. In other non-limiting embodiments, ketamine comprises the structure depicted below in Formula I:



[00072] Ketamine in aqueous solution has been shown to react under accelerated conditions of high temperature and pH by a process which involves initial formation of 1-[(2-chlorophenyl) (15ethylamino) methyl] cyclopentanol ("Compound A"). Thus, the term "Compound A" or "Impurity A" as used herein comprises the structure on the right-hand side of the reaction depicted below:



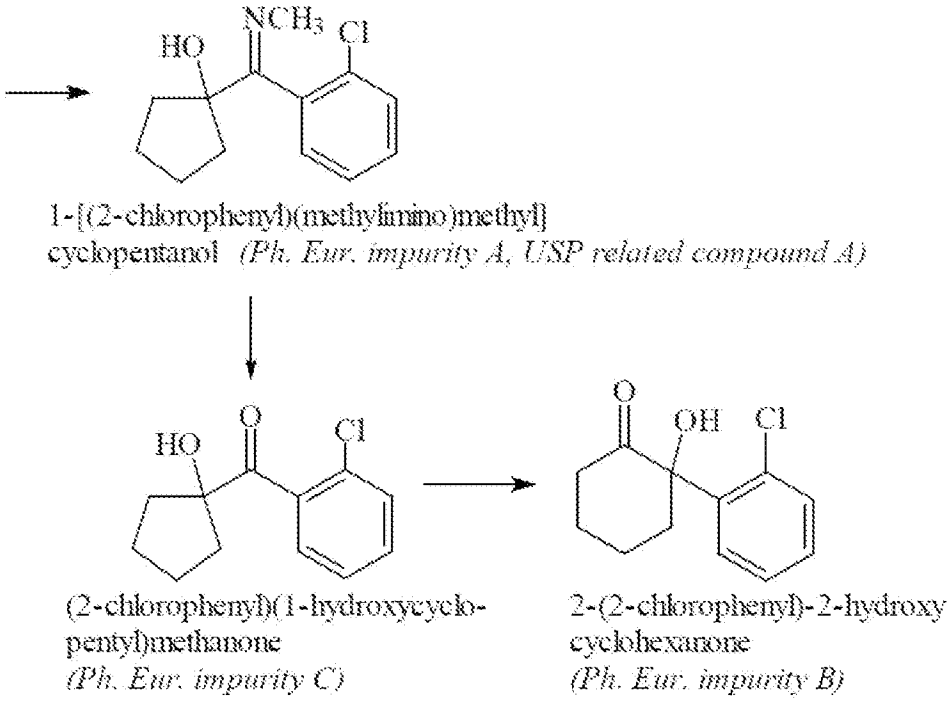
Ketamine

1-[(2-chlorophenyl)(methylimino)methyl] cyclopentanol *(Ph. Eur. impurity A, USP related compound A)*

[00073] Compound A, depending on temperature and pH, may then isomerize back to Ketamine or hydrolyze to the primary product of this reaction: (2-chlorophenyl)(1-hydroxycyclopentyl) methanone 2-(2-chlorophenyl)-2-hydroxycyclohexanone ("Impurity B") which may be major, although not primary product, that results from isomerization of (2-

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chlorophenyl)(1-hydroxycyclopentyl)methanone ("Impurity C"). The structures of "Compound A" (also referred to as "Impurity A"), "Impurity B," and "Impurity C," are depicted in the reaction below:



[00074] The term, "chemically stable," as used herein, refers to a chemical compound which retains its chemical structure and useful properties on a timescale of its expected usefulness. Specifically, the usefulness of the compound is maintained in the environment in which it is stored. Conversely, a compound lacks chemical stability if it decomposes under the conditions of a specific environment. As used herein in certain embodiments, "chemically stable" may mean resistant to degradation of ketamine into its known or unknown decomposition elements. The level of ketamine identified impurity that is acceptable can be up to 0.15% of the formulation as per the ICH guidelines for shelf-life determination, but in certain preferred embodiments, the amount of impurities is lower, *e.g.*, less than 0.05% of the formulation.

[00075] As used herein, the terms "premix", "premixed", or "premixture" refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of ketamine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

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[00076] As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

[00077] As used herein, the term "container closure system" refer to the sum of packaging components that together contain and protect the dosage form, including primary packaging components and secondary packaging components.

[00078] As used herein, the terms "primary packaging components," "primary packaging" means packaging components that are or may be in direct contact with the dosage form. For example, the primary packaging may be an infusion bag, including a flexible film component, one or more ports, and a closure system.

[00079] The terms "infusion bag," "intravenous bag," and "IV bag" may be used interchangeably herein and refer to a type of primary packaging, which comprises a bag film, port(s) and closure system(s). Such infusion bags may be used to administer intravenous infusion products.

[00080] The term "infusion container" as used herein refers to a type of primary packaging used to administer intravenous infusion products, for example, a flexible infusion bag, a semi-flexible plastic infusion container, a prefilled syringe, etc.

[00081] As used herein, the term "flexible" refers to a material that has the ability to deform and return to its original shape when the applied stress is removed without breaking or damage at around standard temperature and pressure (STP), for example about 0 °C ± 40 °C and 1 atm ± 0.005 atm. Flexible materials are distinguished from rigid materials such as glass. A "flexible" infusion bag allows fluid to drain out of the bag without venting. A "flexible" infusion bag may have port tubes and/or closures that are made of rigid or semi-rigid materials, provided that the bag film is flexible.

[00082] As used herein, the terms "secondary packaging components" and "overwrap" refer to a packaging component that is intended to provide additional protection to the drug product but is not typically in direct contact with the dosage form during storage.

[00083] As used herein, the terms "subject" or "patient" refer to a human, a non-human mammal or a non-human animal. The compounds and compositions of the present disclosure have

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application in veterinary medicine as well as for humans, e.g., for the treatment of domesticated species such as canine, feline, and various other pets; farm animal species such as bovine, equine, ovine, caprine, porcine, etc.; wild animals, e.g., in the wild or in a zoological garden; and avian species, such as chickens, turkeys, quail, songbirds, etc.

[00084] As used herein, the terms "pharmaceutical composition" or "pharmaceutical formulation" relates to compositions that can be formulated in any conventional manner using one or more pharmaceutically acceptable diluents or excipients. A "pharmaceutically acceptable" solvent, diluent or excipient, as used herein, means approved by a regulatory agency of the federal or a state government, or as listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans. Suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions).

[00085] As used herein, the terms "therapeutically effective dose," "dose," "effective amount," and "therapeutically effective amount" refer to an amount sufficient to produce the desired effect, which can be readily determined according to standard good medical practice by those of skill in the art. In other non-limiting embodiments, a therapeutically effective dose or effective amount may be any amount that produces a response that a user (e.g., a clinician) will recognize as an effective response to the therapy. Thus, a therapeutically effective amount will generally be an amount that induces a desired effect, such as, for example, sedation or analgesia.

[00086] As used herein, the terms "about" and "approximately" mean +/−20% of the recited value, or within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system.

[00087] As used herein, the terms "intensive care unit" or "ICU" refer to any setting that provides intensive care.

[00088] As used herein, the terms "port," "tubing port," or "port tube" refer to a connector which is sealed into the container portion of an infusion bag. An infusion bag may include one or more ports. The ports may include administrative and/or additive ports. The ports of the invention use commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization. The ports may be coextruded.

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[00089] As used herein, the term "closure" refers to a component that closes or seals a container. A closure provides an effective barrier against microbial contamination. In some aspects, the closure is a twist off closure. The closures referred to herein may comprise commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization.

[00090] As used herein, singular forms, including the singular forms "a" "an" and "the", specifically also encompass the plural referents of the terms to which they refer unless the context clearly dictates otherwise. In addition, as used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

[00091] As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

Pharmaceutical Formulations

[00092] The compounds and compositions of the invention may be formulated as pharmaceutical compositions by admixture with pharmaceutically acceptable solvents and excipients. For example, suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions). In certain non-limiting embodiments, the compounds or compositions are provided in a therapeutically effective amount to an animal, such as a mammal, preferably a human, in need of treatment therewith for inducing a sedative, anxiolytic, analgesic, or anesthetic effect.

[00093] In certain non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is the only therapeutically active ingredient present in the composition. In another non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is formulated in combination with at least one or more other

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therapeutically active ingredient. The formulation is suitable for parenteral administration, such as intravenous administration.

[00094] The pharmaceutical formulations suitable for injectable use, such as, for example, intravenous administration, include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. Solvents or dispersion mediums suitable for stable pharmaceutical formulations include, for example, water for injection (WFI), saline, aqueous dextrose, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and oils. In certain aspects, the solvent may be sterile WFI, 0.9% sodium chloride injection (normal saline), or 5% dextrose in water. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like. Exposure to potential microorganisms such as bacteria, viruses, and fungi can also be prevented using terminal sterilization of prefilled parenteral pharmaceutical products and packages or aseptic processing throughout the manufacturing process of the ketamine product.

[00095] Pharmaceutical formulations may include isotonicity adjusting agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions may be prepared by incorporating the ketamine in the required amounts in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtering and/or terminal sterilization.

[00096] Pharmaceutical formulations may include one or more excipients. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer; amino acids; urea; alcohols; ascorbic acid; phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrrolidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine; lipids; preservatives; suspending agents; stabilizers; and dyes. The term "stabilizer" refers to a compound optionally used in the pharmaceutical compositions of the present invention in order to increase storage life. Non-limiting examples of stabilizers include

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antioxidants. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers.

[00097] Pharmaceutical formulations may include a non-ionic surfactant. Preferred non-ionic surfactants include Polysorbate 20, Polysorbate 80, Triton X-100, Triton X-114, Nonidet P-40, Octyl α-glucoside, Octyl β-glucoside, Brij 35, Pluronic, and Tween 20.

Methods of Using Ready to Use Ketamine Compositions

[00098] As noted above, the methods of treatment of the invention are directed to methods of analgesia in a patient in need thereof comprising administration of ketamine to the patient, wherein the ketamine is administered in an amount effective to produce the desired effect.

[00099] The ketamine for use in the invention can be administered via any suitable route. In a non-limiting embodiment, the therapeutic compound can be delivered in a controlled or sustained release system. For example, a compound or composition may be administered using intravenous infusion, continuous infusion, or other modes of administration. In certain non-limiting embodiments, the dosage of ketamine can be individualized and titrated to the desired clinical effect.

[000100] The present disclosure includes the following non-limiting list of items:

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is free of benzethonium chloride, and wherein the ketamine product is sterile and ready-to-use (RTU).

2. The ketamine product of item 1, wherein the ketamine product has been terminally sterilized.

3. The ketamine product of any preceding item, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.

4. The ketamine product of any preceding item, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.

5. The ketamine product of any preceding item, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerine, mannitol, potassium chloride, or any combination thereof.

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6. The ketamine product of any preceding item, wherein the aqueous ketamine solution comprises 0.9% sodium chloride.

7. The ketamine product of any preceding item, further comprising a pH adjusting agent.

8. The ketamine product of item 7 wherein the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof.

9. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3 to 6.

10. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3.5 to 5.5.

11. The ketamine product of any preceding item, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.

12. The ketamine product of any preceding item, wherein the solution comprises one or more of a chelating agent, an antioxidant, a stabilizer, or a complexing agent.

13. The ketamine product of any preceding item, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.

14. The ketamine product of any preceding item, wherein aqueous ketamine solution is formulated as a total volume of about 50- 500 mL.

15. The ketamine product of any one of items 11-14, wherein the at least one port comprises a plastic material.

16. The ketamine product of item 15, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.

17. The ketamine product of any one of items 11-16, wherein the closure comprises a plastic material.

18. The ketamine product of any one of items 11-17, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts.

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19. The ketamine product of item 18, wherein the twist-off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, and a superior part of the membrane in contact with a zone that forms an air chamber into the closure.

20. The ketamine product of any one of items 18 to 19, wherein the twist-off closure comprises at least one layer of polypropylene.

21. The ketamine product of any one of items 18 to 20, wherein the twist-off closure comprises at least one layer of polyethylene.

22. The ketamine product of any one of items 11-21, wherein the port comprises at least one layer of block copolymer.

23. The ketamine product of any one of items 11-22, wherein the port comprises more than one layer of a block copolymer.

24. The ketamine product of any one of items 11-23, wherein the port comprises more than one layer of a polyolefin block copolymer.

25. The ketamine product of any one of items 11-24, wherein the infusion bag comprises a flexible multilayer film.

26. The ketamine product of any one of items 11-25, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin, polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, or any combination thereof.

27. The ketamine product of any one of items 11-26, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer.

28. The ketamine product of any one of items 11-27, wherein the infusion bag comprises a flexible multilayer film comprising polypropylene styrene-block copolymer.

29. The ketamine product of any one of items 11-28, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

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30. The ketamine product of any one of items 11-29, wherein the infusion bag comprises a 3-layer film comprising polypropylene styrene-block copolymer.

31. The ketamine product of any one of items 11-30, wherein the infusion bag is contained within an overwrap.

32. The ketamine product of item 31, wherein the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof.

33. The ketamine product of any one of items 31 to 32, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

34. The ketamine product of any preceding item, wherein the ketamine product has been autoclaved.

35. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

36. The ketamine product of item 35, wherein the ketamine is at a concentration of about 1 to about 2 mg/mL.

37. The ketamine product of any preceding item, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature.

38. The ketamine product of item 37, wherein the controlled room temperature is 15–30°C.

39. The ketamine product of any preceding item, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

40. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months.

41. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 25 μm does not exceed 60 per container following storage of the ketamine product at room temperature for 24 months.

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42. The ketamine product of any preceding item, wherein the total impurities in the aqueous ketamine solution is less than or equal to 1%.

43. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%.

44. The ketamine product of any preceding item, wherein the bacterial endotoxin content is less than 0.4 EU/mg.

45. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater compared to the ketamine content before storage.

46. The ketamine product of any preceding item, containing about 250 mg ketamine hydrochloride.

47. The ketamine product of any preceding item, containing about 500 mg ketamine hydrochloride.

48. A method of preparing the ketamine product of any preceding item, comprising:

    i) adding ketamine or a pharmaceutically acceptable salt thereof to water;

    ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent;

    iii) filtering the solution of step (ii);

    iv) filling the solution of step (iii) into an infusion bag; and

    v) terminally sterilizing the infusion bag of step (iv).

49. The method of item 48 further comprising overwrapping the terminally sterilized infusion bag with an overwrap.

50. The method of any one of items 48-49, wherein the terminal sterilization comprises autoclaving the infusion bag.

51. The method of item 50, wherein said autoclaving is at a temperature ranging from 110 to 130° C for a period of time ranging from 7 to 60 minutes.

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52. The method of any one of items 50-51, wherein said autoclaving is at a temperature of 121° C for a period of time ranging from 7 to 60 minutes.

53. The method of any one of items 50-52, wherein said autoclaving is at a temperature of 121° C for about 15 minutes.

54. The method of any one of items 50-53, wherein the method comprises overwrapping the infusion bag of step (iv) prior to terminally sterilizing the infusion bag.

55. A method of treating a subject in need of analgesia, comprising administering the ketamine product of any one of items 1-47 to the subject as a continuous infusion.

56. The method of item 55, wherein the ketamine solution is administered by intravenous infusion.

57. The method of item 55 or item 56, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.

58. The method of item 55 or item 56, wherein the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

59. The method of item 55 or item 56, wherein the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

60. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

EXAMPLES

[000101] The following examples are merely illustrative of the presently disclosed subject matter and they should not be considered as limiting the scope of the present disclosure in any way.

Example 1: Exemplary Formulations

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[000102] In one embodiment, the ketamine product comprises the composition of Table 1.

TABLE 1

Ketamine Hydrochloride in Sodium Chloride Injection 1 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine as Ketamine HCl	1 mg/mL 1.15 mg/mL	250 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000103] In another embodiment, the ketamine product may comprise the composition of Table 2.

TABLE 2

Ketamine Hydrochloride in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine as Ketamine HCl	2 mg/mL 2.3 mg/mL	500 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000104] In another embodiment, the ketamine product may comprise the composition of Table 3.

TABLE 3

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Ketamine in Sodium Chloride Injection 1 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine (free base)	1 mg/mL	250 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000105] In another embodiment, the ketamine product may comprise the composition of Table 4.

TABLE 4

Ketamine in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	**Quantity per Unit (mg/mL)**	**Quantity per Unit (250 mL container)**	**Function**	**Reference Standard**
Ketamine (free base)	2 mg/mL	500 mg	API	USP
Excipient(s)				
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

[000106] The inventors contemplate that additional ketamine products may be provided in different volumes with the same proportion of components as listed in Tables 1-4 above. Further, the inventors contemplate that other solvent systems may be substituted for the sodium chloride and water for injection. As one example, 5% dextrose in water for injection may be used in place of sodium chloride in water for injection in the formulations above. Further the inventors contemplate that any pharmaceutically acceptable salt of ketamine may be used in the formulations

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above, using the concentration of ketamine as the free base listed in Tables 3 and 4 above. The ketamine formulations above beneficially do not require an antimicrobial such as benzethonium chloride. The ketamine formulations above beneficially do not require any preservative. Nonetheless, the inventors contemplate that one or more excipients, such as a chelating or complexing agent or an antioxidant, may be added to the formulation without reducing the stability of the ready-to-use ketamine product described herein.

Example 2: Study of Stability Following Terminal Sterilization

[000107] Batches of the ketamine solution with the formulations described in Table 1 (1 mg/ml) and Table 2 (2mg/ml) were manufactured to study the effect of terminal sterilization by autoclaving on product behavior. The primary packaging for each formulation included an infusion bag comprising a flexible multilayer film comprising a 3-layer polypropylene styrene-block copolymer based film (APP114S film manufactured by Polycine); a tube port comprising a multilayer polyolefin and styrene block copolymer tube material (APP107 manufactured by Polycine); and a twist off closure composed of low density polyethylene (LDPE) and polypropylene (PP). The closure comprised a membrane that created a barrier, wherein the inferior part of the membrane was in direct contact with the ketamine solution, while the superior part was in contact with a zone that forms an air chamber into the closure. Autoclaving of the primary packaging filled with the preservative-free ketamine formulations of Table 1 (1 mg/ml) and Table 2 (2 mg/ml), respectively, was conducted at a target temperature T= 121°C± 1°C and time at F0=15 according to USP <1222>, which is incorporated fully herein.

[000108] The objective of this study was to evaluate the quality of ketamine formulation seven days after the product is exposed to terminal sterilization processes at 121°C at different F=0. Only slight, not significant, pH decrease was noted. There was no significant variation on assay (%) of ketamine from before to after sterilization.

TABLE 5: Assay and pH before vs after sterilization

Product	**Ketamine Formulation 1mg/ml**			**Ketamine Formulation 2mg/ml**		
Batch	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Average Assay pre-sterilization (% of Ketamine base)	100.6	101.5	100.9	100.1	101.7	100.0
Assay post-sterilization (FP) (% of labelled amount of Ketamine base)	100.5	101.7	100.6	100.6	101.7	100.5
Extractable volume (ml)	251	252	251	252	251	252

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Product	Ketamine Formulation 1mg/ml			Ketamine Formulation 2mg/ml		
Batch	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Assay post-sterilization (FP) (%of Ketamine base)	100.1	100.9	100.2	99.8	101.3	99.7
Assay % change post- VS pre-sterilization	**-0.5**	**-0.6**	**-0.7**	**-0.3**	**-0.4**	**-0.3**
pH pre-sterilization (end of filling)	5.2	4.8	5.2	4.9	4.8	5.2
pH post-sterilization (FP)	4.6	4.5	4.6	4.6	4.4	4.7
Change in pH (post VS pre-sterilization)	**-0.6**	**-0.3**	**-0.6**	**-0.3**	**-0.4**	**-0.5**

[000109] For the ketamine product with the formulation described in Table 1 (1 mg/ml) the maximum pH decrease after sterilization was equal to 0.6 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.5 pH units.

[000110] For the ketamine product of the disclosure with the formulation described in Table 2 (2mg/ml) the maximum pH decrease after sterilization was equal to 0.5 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.4 pH units.

[000111] The results of Tables 5 show that the ketamine product of the invention can be terminally sterilized using autoclaving at a target temperature T= 121°C± 1°C and time at F0=15 according to USP <1222> without affecting the quality of ketamine formulation.

Example 3: Stability Studies

[000112] The terminally sterilized infusion bags, as described in Example 2, comprising a preservative-free aqueous ketamine solution with the formulation described in Table 1 (1 mg/ml) or Table 2 (2 mg/ml) were compared to a commercially available concentrated ketamine solution product in multi-dose glass vials containing the preservative benzethonium chloride. The commercially available concentrated products were diluted with 0.9% sodium chloride in a glass volumetric flask to achieve a concentration of 1 mg/mL or 2 mg/mL of Ketamine. The results for the 1 mg/ml and 2 mg/ml products are shown in Tables 6 and 7, respectively.

TABLE 6: Accelerated Condition 40 ± 2°C / <25% RH – 6 months

Batch	**Commercial Product Batch 1 (1 mg / mL)**	**Commercial Product Batch 2 (1 mg / mL)**	**Ketamine Product of the Disclosure**	**Ketamine Product of the Disclosure**	**Ketamine Product of the Disclosure**

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Test			Batch 1 (1 mg / mL)	Batch 2 (1 mg / mL)	Batch 3 (1 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	101.2	101.4	100.5	101.7	100.6
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	5.0	5.0	4.7	4.5	4.8
Osmolality (mOsmol/kg)	291	286	296	298	296

TABLE 7: Accelerated Condition 40 ± 2°C / <25% RH- 6 months

Batch	Commercial Product Batch 1 (2 mg / mL)	Commercial Product Batch 2 (2 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

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Test			Batch 1 (2 mg / mL)	Batch 2 (2 mg / mL)	Batch 3 (2 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.2	100.7	100.4	101.5	100.4
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.6
Osmolality (mOsmol/kg)	297	288	304	305	304

TABLE 8: Long term Condition 25 ± 2°C / 40 ± 5 % RH – 12 months

Batch	Commercial Product Batch 1 (1 mg / mL)	Commercial Product Batch 2 (1 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

Par Health Inc. Ex. 1002-0124

Test			Batch 1 (1 mg / mL)	Batch 2 (1 mg / mL)	Batch 3 (1 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.9	102.1	100.5	101.9	100.7
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	0.05	0.06
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	0.05	0.06
pH (pH Units)	5.1	5.0	4.8	4.5	4.8
Osmolality (mOsmol/kg)	287	290	293	294	295

TABLE 9: Long term Condition 25 ± 2°C / 40 ± 5 % RH – 12 months

Batch	Commercial Product Batch 1 (2 mg / mL)	Commercial Product Batch 2 (2 mg / mL)	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure	Ketamine Product of the Disclosure

Par Health Inc. Ex. 1002-0125

Test			Batch 1 (2 mg / mL)	Batch 2 (2 mg / mL)	Batch 3 (2 mg / mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.3	102.3	100.5	101.7	100.6
Impurities:					
Specified identified impurity- Impurity A (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity B (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Specified identified impurity- Impurity C (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Unspecified unidentified impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Total impurity (%)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.8
Osmolality (mOsmol/kg)	287	299	301	303	303

[000113] After 6 months of stability testing at 40°C, there was no observed variation in the pH and in the color of the ketamine products of the disclosure contained in ready-to-use, terminally sterilized, infusion bags. After 6 months at 40°C there was no observed reduction in Ketamine Hydrochloride Assay compared to T=0 sterilized. The total impurities of the preservative-free

Par Health Inc. Ex. 1002-0126

ketamine formulations of the disclosure, packaged in ready-to-use, terminally sterilized, infusion bags were comparable with the results obtained at T= 0.

[000114] The results of Tables 6-9 surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride under accelerated conditions and long-term storage. While the average pH of ketamine solution in infusion bags seen in the experiment was 4.5 - 4.8 pH units and the average pH of the commercially available product when diluted for use was 4.9 - 5.2, the ketamine solution in infusion bags remained stable. Additionally, osmolality of ketamine solution in infusion bags seen in the experiment was comparable to the commercially available product, and both were inside the physiological range (according to the USP <785>, which is incorporated fully herein, the osmolality of blood ranges between 285 and 310 mOsmol/kg) and therefore comparable in the context of this evaluation. No significant change was noted during the stability studies and no degradation was detected despite of a lack of any antimicrobial, stabilizer or preservative in the ketamine products of the present disclosure.

Example 4: Stress Studies

[000115] The ketamine product of the disclosure was analyzed to evaluate critical product characteristics /parameters under stressed conditions. Stress testing was intended to identify the likely degradation products, which further helped in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used.

[000116] An oxidative stress study was conducted in accordance with the procedure set out in Fig. 1. The results for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:1 are shown in Tables 10 and 11, respectively, where "Δ" refers to the difference between the test batch and the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:1 ratio. The oxidative degradation 1:1 reported data was collected 72 hours after addition of the hydrogen peroxide.

TABLE 10: Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:1 with H_2O_2

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Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (1 mg/ml)**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.74	4.58	- 0.16
Osmolality	270 - 330	mOsmol/Kg	296	295	- 1
Assay	95.0-105.0	%	100.0	99.6	- 0.4
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 0 0

TABLE 11: Oxidative degradation results of ketamine solution 500 mg/250 mL (2 mg/ml) in ratio 1:1 with H_2O_2

Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (2 mg/ml)**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	-

Par Health Inc. Ex. 1002-0128

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Appearance of solution - Clarity	Clear	-	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.60	4.56	- 0.04
Osmolality	270 - 330	mOsmol/Kg	299	308	+ 9
Assay	95.0-105.0	%	99.7	99.6	- 0.1
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 0 0

[000117] The results shown in Tables 10-11 demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed after 72 hours after the ketamine solution was treated with hydrogen peroxide in stoichiometric ratio 1:1.

[000118] The results of the oxidative stress for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:10 are shown in Tables 12 and 13, respectively, where "Δ" refers to the difference between the blank sample and Batch 1. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:10 ratio. The reported data was collected 48 hours after addition of the hydrogen peroxide.

TABLE 12: Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Assay	95.0-105.0	%	100.2	99.2	- 1.0

Par Health Inc. Ex. 1002-0129

Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (1 mg/ml)**	**Δ**
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity RT 5.3	NMT 0.20	%	< 0.05	0.13	+ 0.13
- Unspecified unidentified impurity RT 9.0	NMT 0.20	%	< 0.05	0.14	+ 0.14
- Total impurities	NMT 1.0	%	< 0.05	0.27	+ 0.27

TABLE 13: Oxidative degradation results of ketamine solution 500 mg/250 mL in ratio 1:10 with H_2O_2

Test	**Specifications**	**Unit**	**Blank sample**	**Test Batch (2 mg/ml)**	**Δ**
Assay	95.0-105.0	%	100.1	99.5	- 0.6
Impurities:					
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	0
- Unspecified unidentified impurity RT 5.3	NMT 0.20	%	< 0.05	0.08	0.08
- Unspecified unidentified impurity RT 9.0	NMT 0.20	%	< 0.05	0.08	0.08
- Total impurities	NMT 1.0	%	< 0.05	0.16	0.16

Par Health Inc. Ex. 1002-0130

[000119] The results shown in Tables 12-13 demonstrate that there was a slight increase in impurities in the ketamine solution after 48 hours after the ketamine solution was treated with hydrogen peroxide in ratio 1:10.

[000120] An acid/alkaline study was conducted in accordance with the procedure set out in Fig. 2. These results demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed through one month of observation (t=1M) compared to the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) at pH 4.7, while the "test batch" refers to the formulation at varying test pH.

TABLE 14: Degradation results of ketamine solution 250 mg/250 mL at pH 2.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	2.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	300	-
Assay	95.0-105.0	%	100.3	100.4	100.0	100.2	100.4
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

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Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Particulate matter: - ≥ 10 micron - ≥ 25 micron	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

TABLE 15: Degradation results of ketamine solution 250 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	3.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	294	-
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter:	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

Par Health Inc. Ex. 1002-0132

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
- ≥ 10 micron - ≥ 25 micron							

TABLE 16: Degradation results of ketamine solution 250 mg/250 mL at pH 5.5

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	3.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	294	-
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

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TABLE 17: Degradation results of ketamine solution 250 mg/250 mL at pH 6.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	NA*	pH Units	4.7	-	-	6.5	-
Osmolality	270 - 330	mOsmol/Kg	293	-	-	295	-
Assay	95.0-105.0	%	100.23	100.3	100.3	100.4	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 18: Degradation results of ketamine solution 500 mg/250 mL at pH 2.5

Par Health Inc. Ex. 1002-0134

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	2.48	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	309	-
Assay	95.0-105.0	%	100.1	100.7	100.3	100.2	100.5
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 19: Degradation results of ketamine solution 500 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-

Par Health Inc. Ex. 1002-0135

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	3.51	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	305	-
Assay	95.0-105.0	%	100.1	100.4	100.1	100.0	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 1 0

TABLE 20: Degradation results of ketamine solution 500 mg/250 mL at pH 5.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-

Par Health Inc. Ex. 1002-0136

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-
pH	3.5 - 5.5	pH Units	4.63	-	-	5.51	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	303	-
Assay	95.0-105.0	%	100.1	100.2	100.2	100.2	100.1
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	-	-	 0 0	 0 0

TABLE 21: Degradation results of ketamine solution 500 mg/250 mL at pH 6.5

Test	**Specifications**	**Unit**	**Blank sample**	**t=24h**	**t=48h**	**t=72h**	**t=1M**
Completeness of Solution	Free from visible particles	-	Free from visible particles	-	-	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	-	-	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	-	-	Clear	-

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Test	Specifications	Unit	Blank sample	t=24h	t=48h	t=72h	t=1M
pH	3.5 - 5.5	pH Units	4.63	-	-	6.50	-
Osmolality	270 - 330	mOsmol/Kg	302	-	-	304	-
Assay	95.0-105.0	%	100.1	100.0	100.2	100.1	100.2
Impurities							
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Particulate matter: - ≥ 10 micron - ≥ 25 micron	NMT 23 NMT 3	N° part/mL	0 0	-	-	0 0	0 0

[000121] A heat degradation study was performed on the ketamine solution in infusion bags in accordance to the procedure set out in Fig. 2. The primary packaging used was the same infusion bags described in Example 2. No significant degradation of the ketamine solution in primary packaging was observed after two terminal sterilization cycles. The pH dropped slightly after each sterilization but it remained within the specification limits. These results demonstrate that the ketamine product of the invention is stable after two sterilization cycles conducted at 121 °C for 15 minutes each, as no significant change is noted in assay or impurity profile.

TABLE 22: Thermal stress results of Ketamine HCl Injection 250 mg/250 mL

Par Health Inc. Ex. 1002-0138

Test	**Specifications**	**Unit**	**Blank sample**	**Sterilization F015**	**Double sterilization F015**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.7	4.5	4.3	- 0.4
Osmolality	270 - 330	mOsmol/Kg	296	292	294	- 2
Assay	95.0-105.0	%	100.0	99.5	98.9	- 1.2
Impurities						
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	N° part/mL	 0 0	 0 0	 1 0	 + 1 0

TABLE 23: Thermal stress results of Ketamine HCl Injection 500 mg/250 mL

Par Health Inc. Ex. 1002-0139

Test	**Specifications**	**Unit**	**Blank sample**	**Sterilization F015**	**Double sterilization F015**	**Δ**
Completeness of Solution	Free from visible particles	-	Free from visible particles	Free from visible particles	Free from visible particles	-
Appearance of solution - Color	Colorless to slightly yellow	-	Complies	Complies	Complies	-
Appearance of solution - Clarity	Clear	-	Clear	Clear	Clear	-
pH	3.5 - 5.5	pH Units	4.6	4.3	4.1	- 0.5
Osmolality	270 - 330	mOsmol/Kg	299	303	300	+ 1
Assay	95.0-105.0	%	99.7	99.4	99.0	- 0.7
Impurities						
- Ketamine related compound A	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Unspecified unidentified impurity	NMT 0.20	%	< 0.05	< 0.05	< 0.05	0
- Total impurities	NMT 1.0	%	< 0.05	< 0.05	< 0.05	0
Particulate matter: - ≥ 10 micron - ≥ 25 micron	 NMT 23 NMT 3	 N° part/mL	 0 0	 0 0	 1 0	 +1 0

Example 5: Manufacturing Process Development

[000122] The ketamine product of the disclosure is an aqueous solution and is terminally sterilized. The manufacturing process involved dissolution of ketamine HCl in water for injection and addition of sodium chloride to adjust for tonicity in accordance to the procedure set out in Fig. 4.

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[000123] Complete dissolution was verified by in process sampling and analysis of bulk solution before terminal sterilization as shown in Figs. 5 and 6 and Table 23.

TABLE 23: Test results of Dissolution

Test	Limits	Units	Dissolution Time	1 mg/mL (as in Table 1)			2 mg/mL (as in Table 2)		
				Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Appearance	Clear, colorless to slightly yellowish solution free from visible particles	n/a	5 min	comply	comply	comply	comply	comply	comply
			10 min	comply	comply	comply	comply	comply	comply
			15 min	comply	comply	comply	comply	comply	comply
pH	*	pH Units	5 min	5.0	4.8	5.3	5.1	4.8	5.2
			10 min	5.0	4.8	5.2	4.9	4.8	5.3
			15 min	5.0	4.7	5.2	5.0	4.8	5.2
Conductivity	14.3 – 15.3 (for information only)	mS/cm	5 min	15.3	15.3	15.3	15.1	15.1	15.0
			10 min	15.3	15.2	15.3	15.2	15.0	15.0
			15 min	15.3	15.2	15.3	14.7	15.0	14.9
Bulk solution Density	1.002 – 1.005 (for information only)	g/mL	5 min	n/a	n/a	n/a	n/a	n/a	n/a
			10 min	n/a	n/a	n/a	n/a	n/a	n/a
			15 min	1.004	1.004	1.004	1.004	1.004	1.004
Ketamine Assay	95.0 – 105.0	% of Ketamine base	5 min	101.9	101.6	100.9	100.7	102.0	100.0
			10 min	101.7	101.4	100.9	100.9	101.8	100.3
			15 min	101.8	101.4	100.9	100.6	102.3	100.1
Sodium Chloride Assay	146.0 – 162.0	mmol/L	5 min	156.9	153.7	154.9	155.9	155.8	154.5
			10 min	157.6	155.7	155.0	156.4	156.2	154.6
			15 min	157.2	156.3	154.6	155.5	156.1	154.7
Osmolality	270 – 330	mOsmol/kg	5 min	299	299	289	302	304	302
			10 min	301	293	293	302	305	302
			15 min	296	294	297	299	305	302

[000124] The ketamine bulk solution was formulated as in Table 1 (1mg/ml) and Table 2 (2mg/ml) then filtered through a pre-filter (3 µm pore size) followed by a filtration through one filter (0.2 µm pore size filters). The in-line filtration was pressure driven (conducted under

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compressed air) and the drug product was then filled into infusion bags through the tube port in line with filtration. Drug product solution compatibility with the filter and robustness of the filling process was confirmed as shown in Fig. 7.

TABLE 24: Filter Compatibility

Filling stop duration	Test	Limits	Units	1 mg/mL		2 mg/mL	
				Batch 1	Batch 2	Batch 4	Batch 5
1 Hour	pH (20÷25°C)	3.5 – 5.5	pH Units	5.3	4.7	4.9	4.8
				5.3	4.7	4.9	4.8
				5.3	4.7	4.9	4.8
	Ketamine Assay	95.0 – 105.0	% of ketamine base	100.7	101.5	99.9	101.3
				100.6	101.6	100.0	101.7
				100.2	101.6	100.2	101.6
2 Hours	pH (20÷25°C)	3.5 – 5.5	pH Units	5.3	4.8	4.9	4.9
				5.3	4.8	4.9	4.8
				5.1	4.8	4.9	4.8
	Ketamine Assay	95.0 – 105.0	% of ketamine base	100.4	101.5	100.1	101.6
				100.5	101.6	100.1	101.6
				100.3	101.4	100.1	101.5

[000125] After filling the infusion bag with the ketamine solution, the tube port was sealed using a twist-off closure. Terminal sterilization was then conducted using the autoclave process described in Example 2. The closure and tube port are thermally sealed due to the autoclave temperature.

[000126] These results demonstrate that the manufacturing process in accordance to the procedure shown in Fig. 4 is compatible with manufacturing the ketamine product of the invention as no significant change is noted in the characteristics of the ketamine solution (such as the ketamine assay, pH, etc.) during the dissolution and filtering steps.

[000127] It is to be understood that any particular aspect of the present disclosure that falls within the prior art may be excluded from any one or more of the claims. Since such aspects are

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deemed to be part of the whole of the present disclosure, any part of the whole disclosure may be excluded even if the exclusion is not set forth explicitly herein. Additionally, it is to be understood that while the present disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and alterations are within the scope of the following claims.

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CLAIMS

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine product is sterile and ready-to-use (RTU).
2. The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.
3. The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. The ketamine product of claim 1, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.
5. The ketamine product of claim 1, wherein the ketamine solution is free of benzethonium chloride.
6. The ketamine product of claim 1, wherein the aqueous ketamine solution has pH of about 3 to about 6.
7. The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
8. The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
9. The ketamine product of claim 7, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
10. The ketamine product of claim 7, wherein the closure comprises a plastic material.
11. The ketamine product of claim 7, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

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12. The ketamine product of claim 10, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

13. The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyolefin, polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

14. The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

15. The ketamine product of claim 7, wherein the infusion bag comprises a 3-layer film comprising polypropylene styrene-block copolymer.

16. The ketamine product of claim 7, wherein the infusion bag is contained within an overwrap.

17. The ketamine product of claim 16, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

18. The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

20. The ketamine product of claim 19, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

21. The ketamine product of claim 1, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

22. The ketamine product of claim 19, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

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23. The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

24. The ketamine product of claim 1, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months; and/or

the average number of particles equal to or greater than 25 μm does not exceed 600 per container following storage of the ketamine product at room temperature for 24 months.

25. The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 99%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 99% or greater compared to the ketamine content before storage.

26. A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

27. The method of claim 26, wherein the step of terminally sterilizing comprises autoclaving the infusion bag at a temperature between about 110 to about 130° C for a period of time of about 7 to about 60 minutes.

28. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

Par Health Inc. Ex. 1002-0146

29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

30. The ketamine product of claim 29, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature between 15–30°C.

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ABSTRACT

The invention relates to a sterile, ready-to-use, stable aqueous solution of ketamine suitable for direct intravenous infusion to a patient in need thereof, wherein the composition is disposed within a sealed infusion container as a premixture. The invention further relates to aqueous solutions of ketamine that are free of antimicrobials such as benzethonium chloride and are shelf-stable. The pharmaceutical compositions can be used, for example, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

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Inventor 1 Remove

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	Sergio		DUSCI	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tresivio	Country of Residence	IT

Mailing Address of Inventor:

Address 1	C/O INFORLIFE SA		
Address 2	Casai		
City	Campascio	**State/Province**	
Postal Code	7748	**Country**	CH

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Title of the Invention	READY-TO-USE KETAMINE PREMIX FORMULATION		
Attorney Docket Number	4830-114US2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	**Suggested Figure for Publication (if any)**	

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Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

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Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

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Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	63513225	2023-07-12

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	INFORLIFE SA		
Mailing Address Information For Applicant:			
Address 1	CASAI		
Address 2			
City	CAMPASCIO	**State/Province**	
Country	CH	Postal Code	7748
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	INFORLIFE SA

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	CASAI		
Address 2			
City	CAMPASCIO	**State/Province**	
Country i	CH	Postal Code	7748
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Aydin H. Harston/			Date (YYYY-MM-DD)	2024-07-11
First Name	Aydin H.	Last Name	Harston, Ph.D.	Registration Number	65,249

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	4830-114US2
	Application Number	
Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Par Health Inc. Ex. 1002-0156

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Sergio DUSCI	Nonprovisional Application Number (if known):	
Title of Invention:	READY-TO-USE KETAMINE PREMIX FORMULATION		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via USPTO patent electronic filing system.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via USPTO patent electronic filing system.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Aydin H. Harston/	Date July 11, 2024
Name (Print/Typed) Aydin H. Harston, Ph.D	Practitioner Registration Number 65,249

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;

2) a federal, state, local, or international agency, in response to its request;

3) a contractor of the USPTO having need for the information in order to perform a contract;

4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;

5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;

6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;

7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;

8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));

9) the Office of Personnel Management (OPM) for personnel research purposes; and

10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

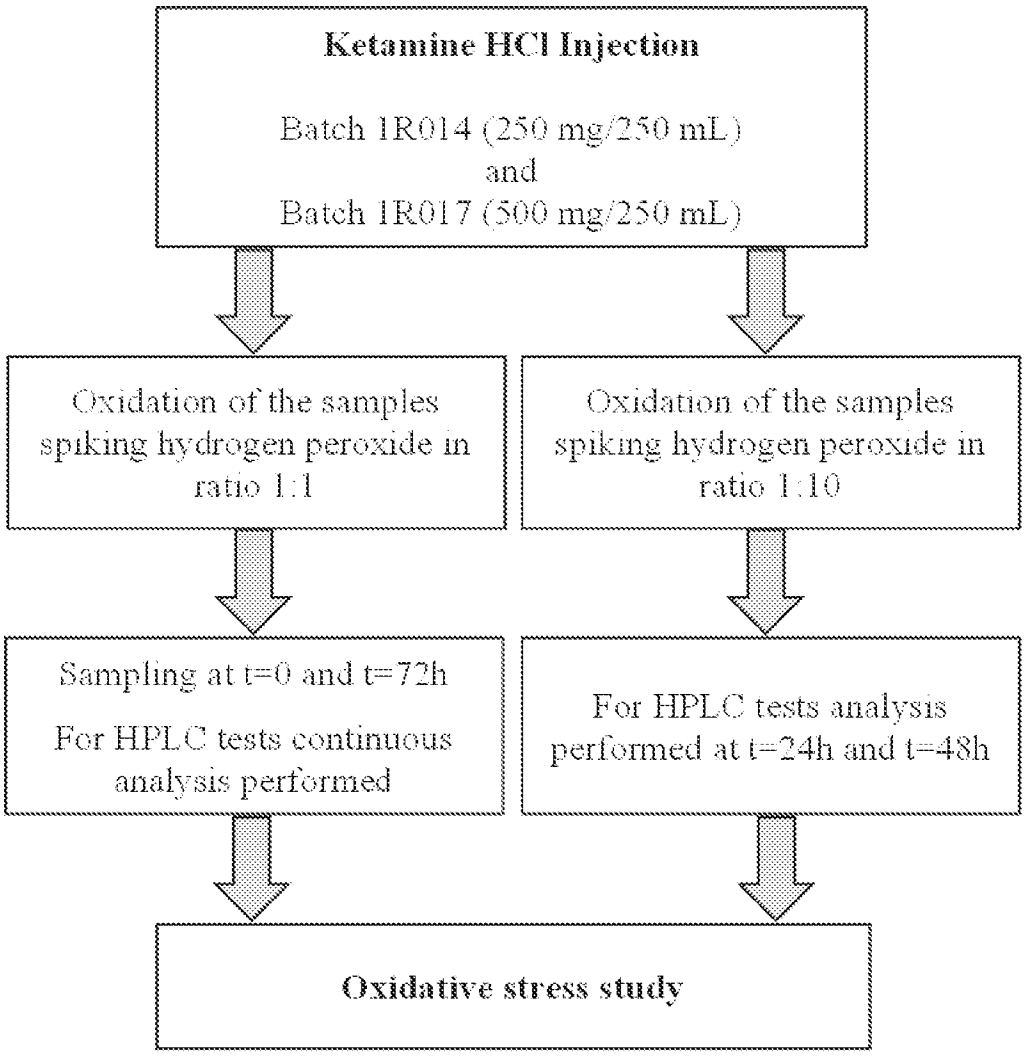

Oxidative Stress study description
Ketamine HCl Injection
Batch 1R014 (250 mg/250 mL)
and
Batch 1R017 (500 mg/250 mL)
Oxidation of the samples spiking hydrogen peroxide in ratio 1:1
Oxidation of the samples spiking hydrogen peroxide in ratio 1:10
Sampling at t=0 and t=72h
For HPLC tests continuous analysis performed
For HPLC tests analysis performed at t=24h and t=48h
Oxidative stress study

Fig. 1

Acid Alkaline stress study description

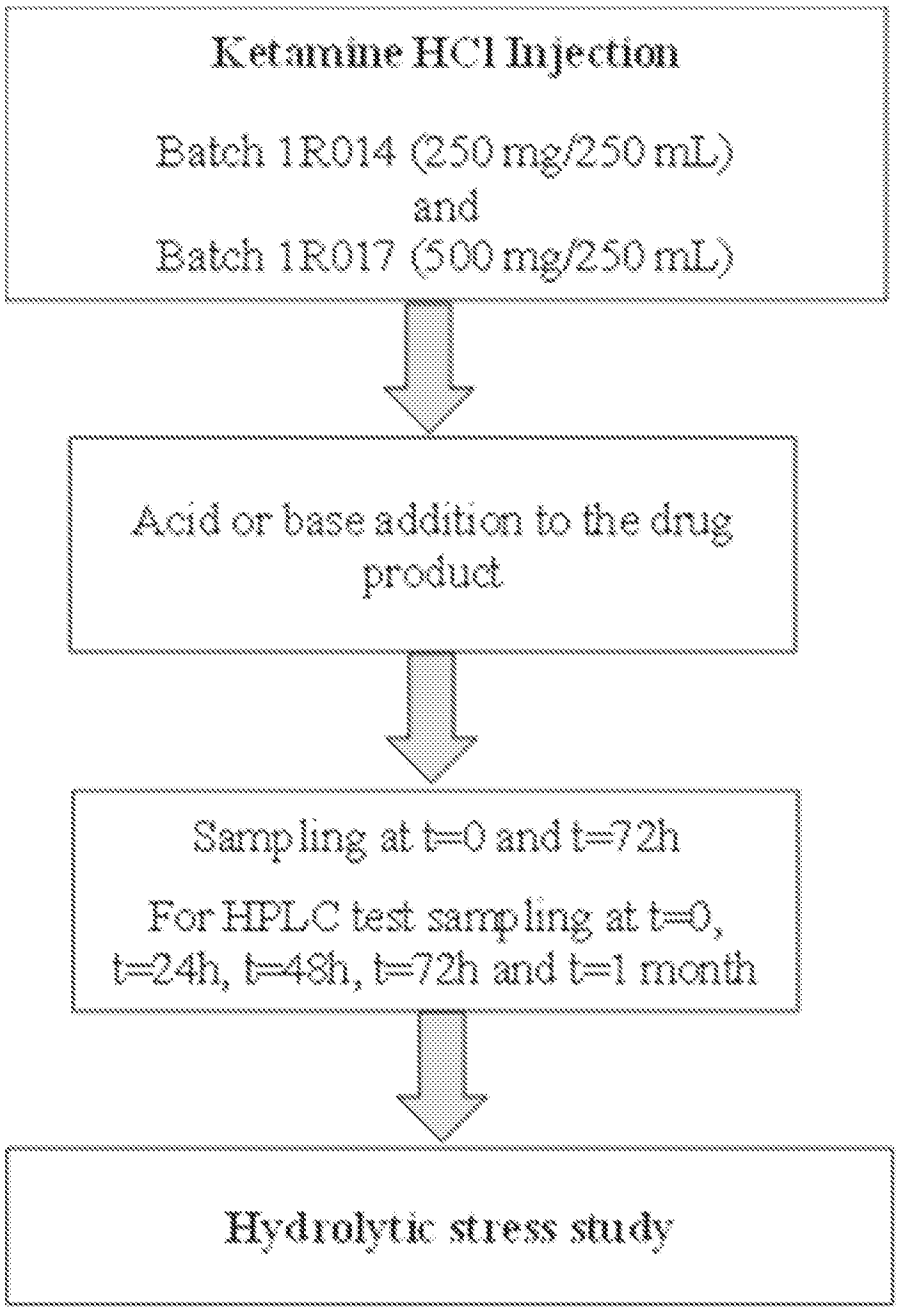


Fig. 2

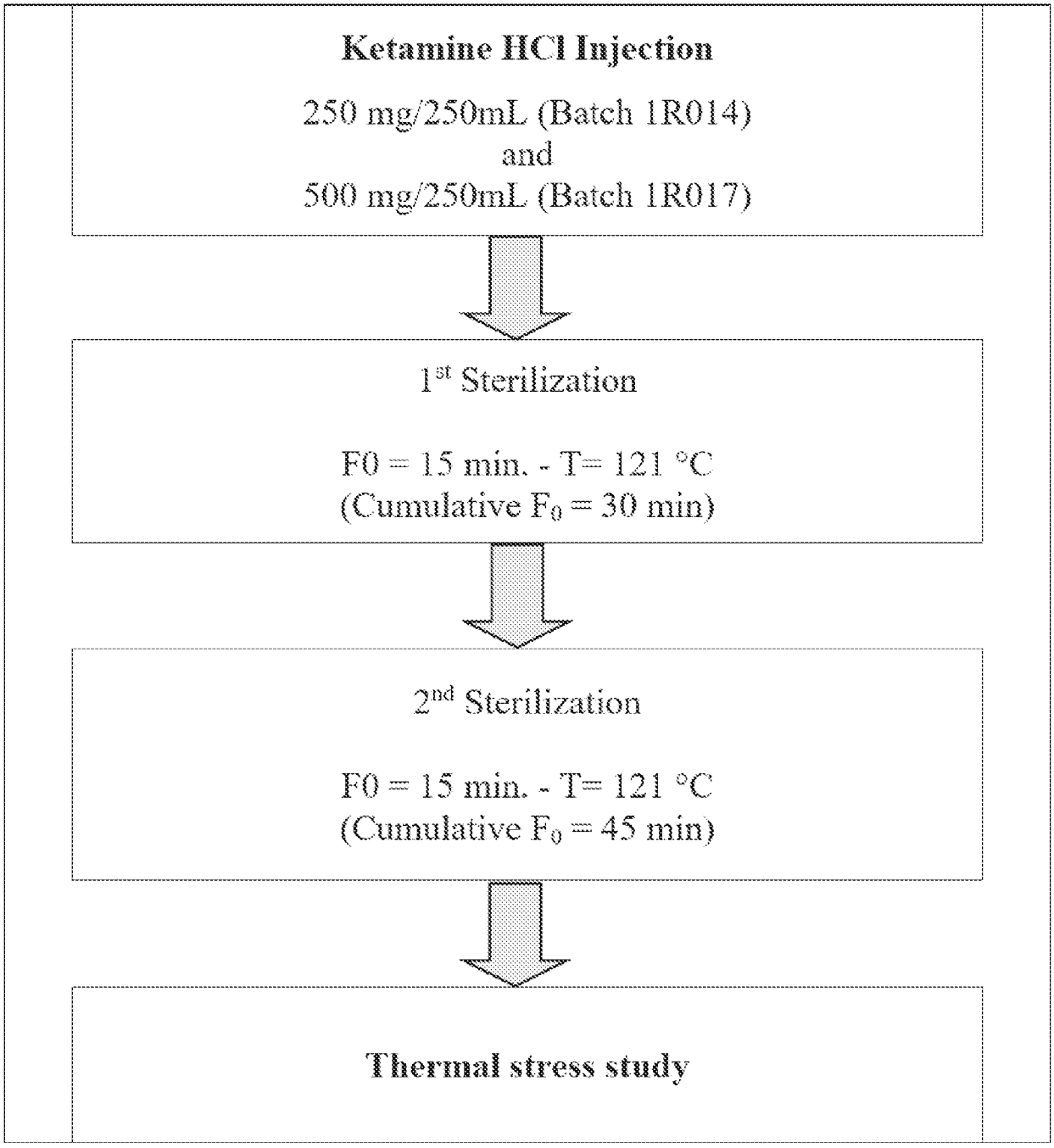

Ketamine HCl Injection
250 mg/250mL (Batch 1R014)
and
500 mg/250mL (Batch 1R017)
1st Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 30 min)
2nd Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 45 min)
Thermal stress study

Fig. 3

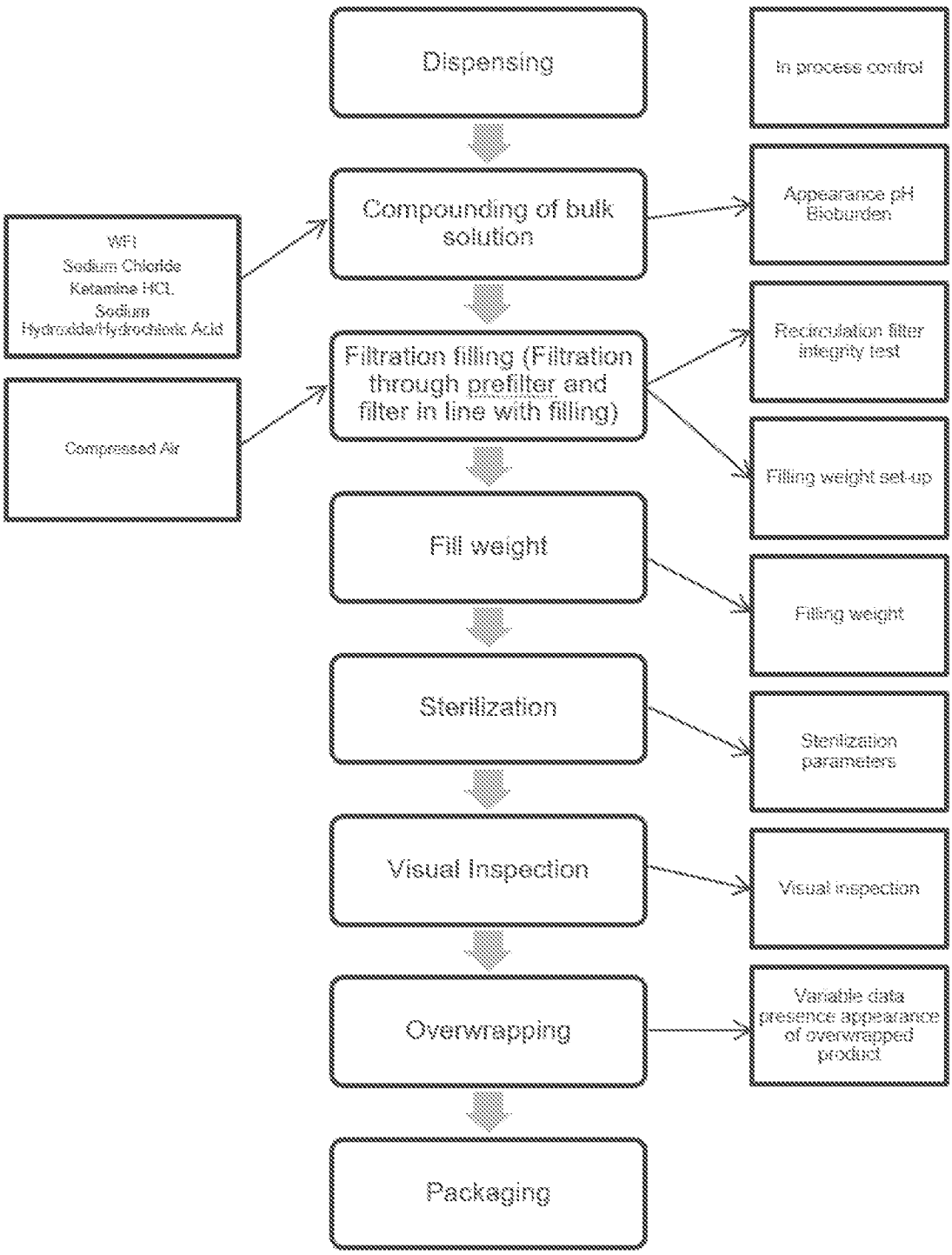

Manufacturing Process
Dispensing
In process control
Compounding of bulk solution
Appearance pH Bioburden
WFI
Sodium Chloride
Ketamine HCL
Sodium Hydroxide/Hydrochloric Acid
Filtration filling (Filtration through prefilter and filter in line with filling)
Recirculation filter integrity test
Compressed Air
Filling weight set-up
Fill weight
Filling weight
Sterilization
Sterilization parameters
Visual Inspection
Visual inspection
Overwrapping
Variable data presence appearance of overwrapped product
Packaging

Fig. 4

Graph 1: Ketamine Injection 1 mg/mL Dissolution Assay

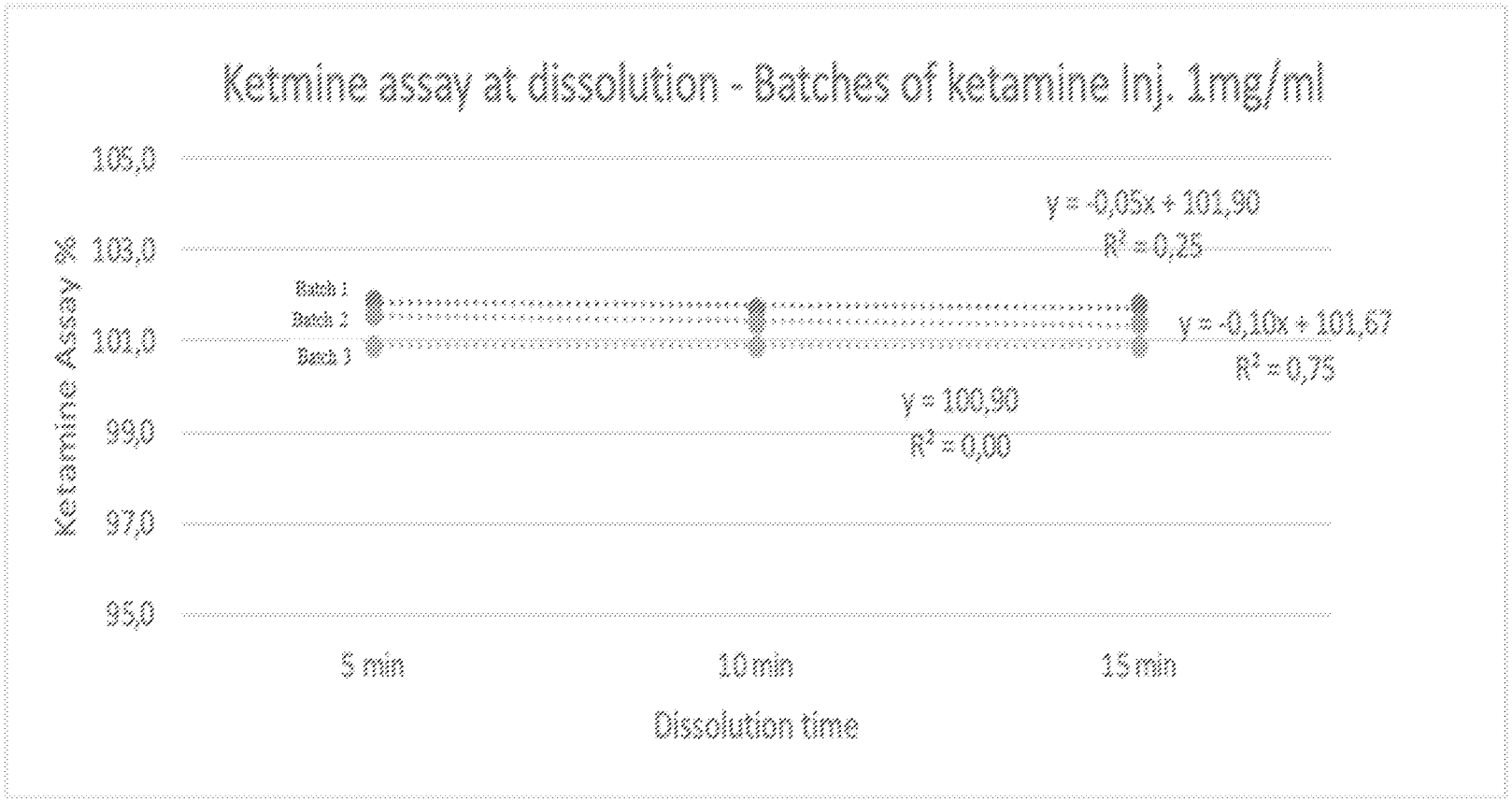


Fig. 5

Par Health Inc. Ex. 1002-0163

Graph 2: Ketamine Injection 2 mg/mL Dissolution Assay

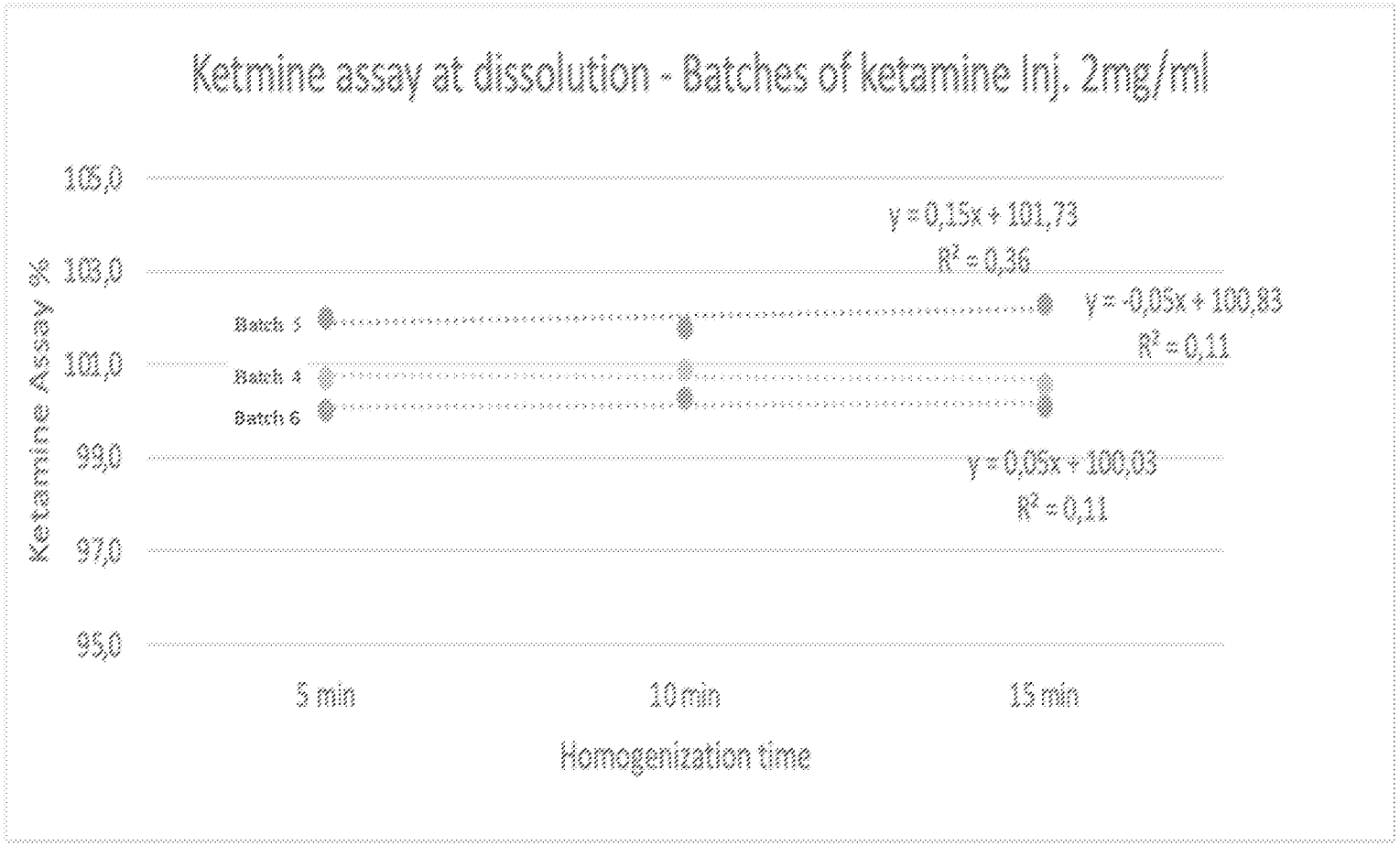


Fig. 6

Par Health Inc. Ex. 1002-0164

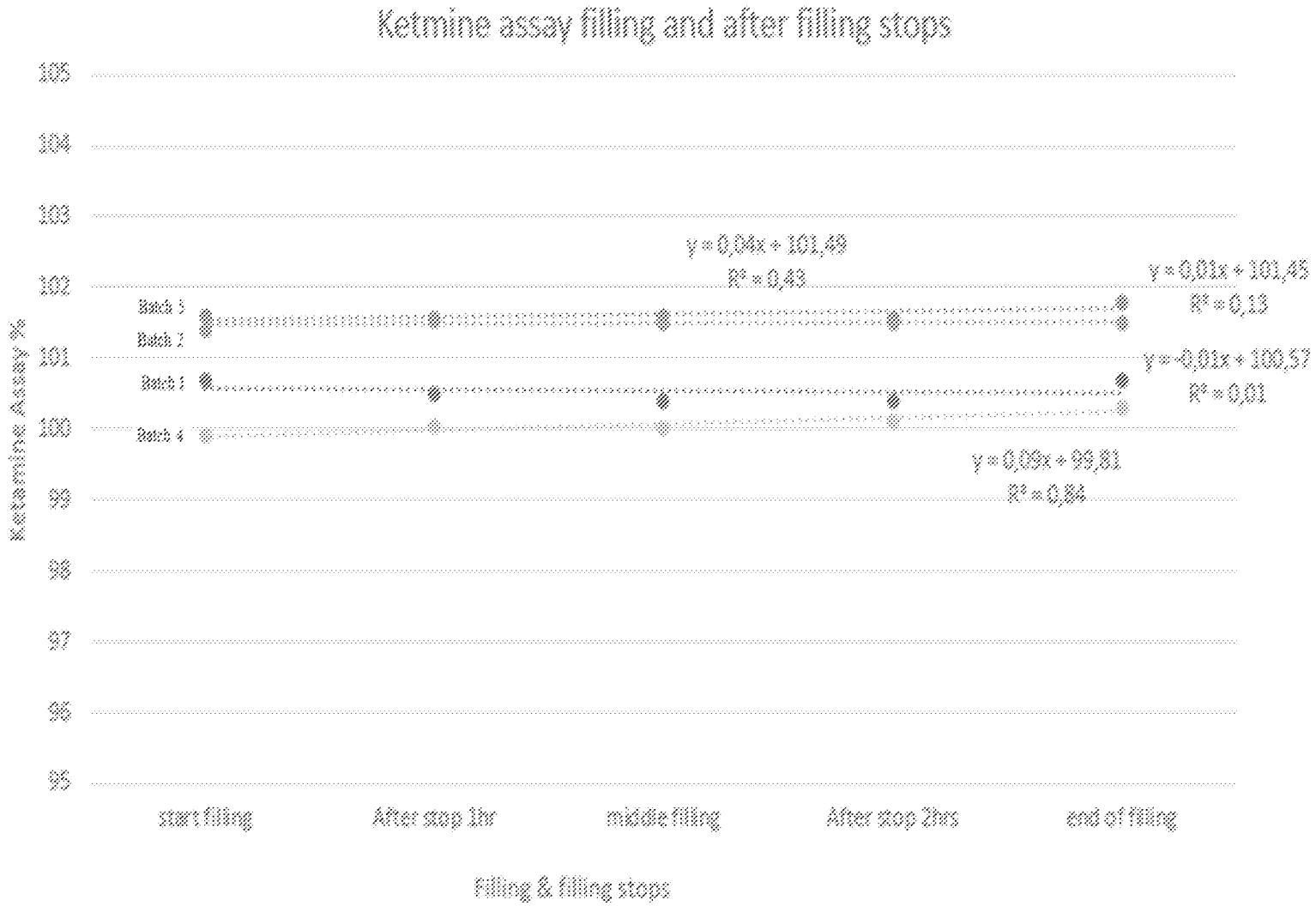


Fig. 7

Par Health Inc. Ex. 1002-0165

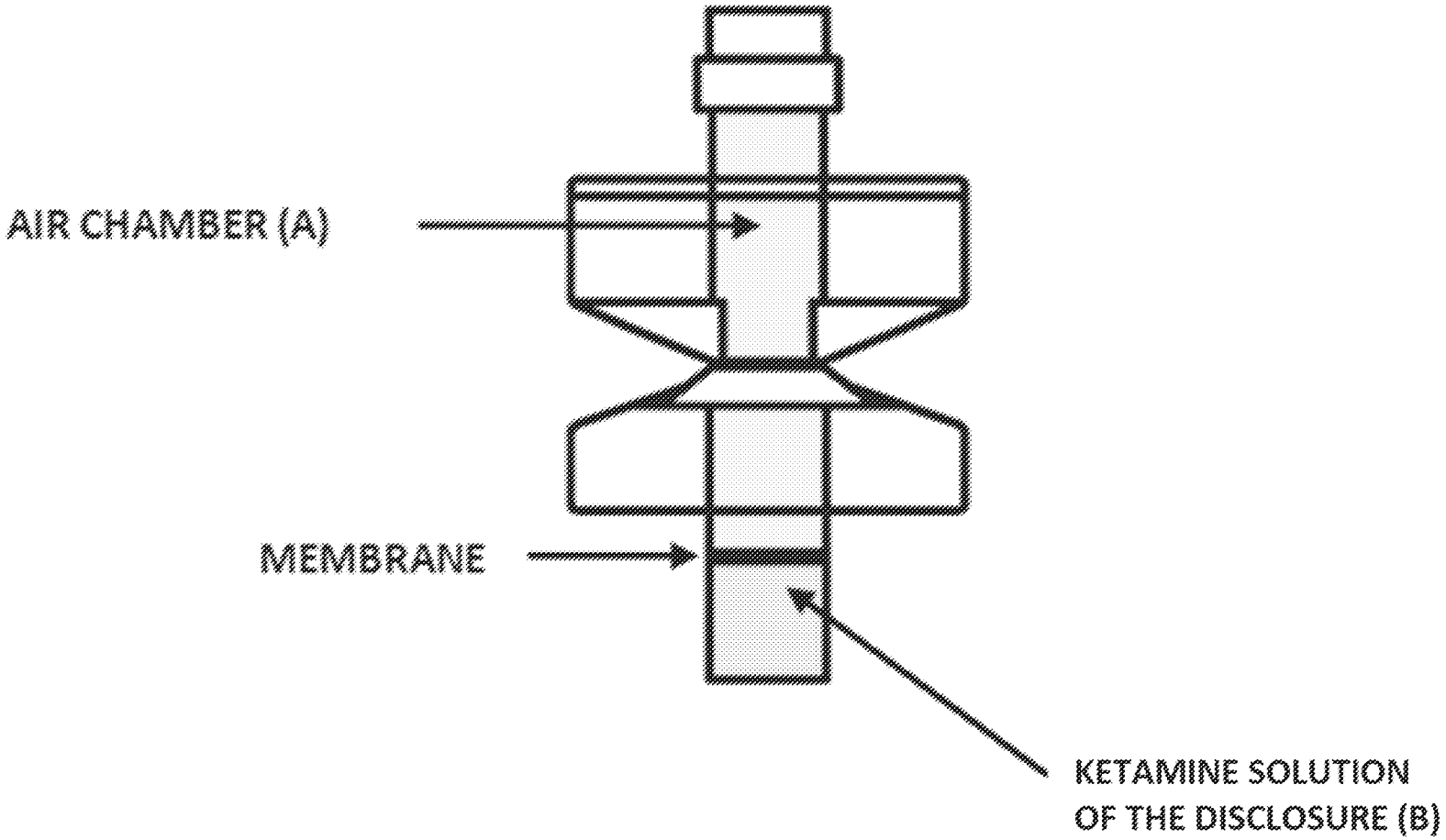

AIR CHAMBER (A)
MEMBRANE
KETAMINE SOLUTION
OF THE DISCLOSURE (B)

Fig. 8

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Caution: *A person may not execute an oath or declaration for an application unless that person has reviewed and understands the contents of the application, including the claims, and is aware of the duty to disclose to the US Patent and Trademark Office all information known to the person to be material to patentability as defined in 37 CFR 1.56.*

Title of Invention	READY-TO-USE KETAMINE PREMIX FORMULATION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Typed Name of Inventor: Sergio DUSCI

Signature of Inventor: Sergio Dusci Date (optional): 07/11/2024

Par Health Inc. Ex. 1002-0167

PTO/AIA/96 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

First Named Inventor/Patent Owner: INFORLIFE SA

Application No./Patent No.: 18770514 Filed/Issue Date: July 11, 2024

Titled: READY-TO-USE KETAMINE PREMIX FORMULATION

INFORLIFE SA, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached*.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached*.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached*.

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PTO/AIA/96 (11-23)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

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The document was recorded in the United States Patent and Trademark Office at

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The document was recorded in the United States Patent and Trademark Office at

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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ *As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Aydin H. Harston/	July 12, 2024
Signature	Date
Aydin H. Harston, Ph.D.	65,249
Printed or Typed Name	Title or Registration Number

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;

2) a federal, state, local, or international agency, in response to its request;

3) a contractor of the USPTO having need for the information in order to perform a contract;

4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;

5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;

6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;

7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;

8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));

9) the Office of Personnel Management (OPM) for personnel research purposes; and

10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**07/12/2024 03:54:09 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	66344658	FILING DATE	-
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Aydin Harston

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-114US2 3.73c Statement.pdf	3	Assignee showing of ownership per 37 CFR 3.73	250 KB
INFORLIFE SA Gen POA.pdf	2	Power of Attorney	170 KB
4830-114US2 Assignment.pdf	2	Assignee showing of ownership per 37 CFR 3.73	3378 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

4830-114US2 3.73c Statement.pdf	AC8DCF18E186D4A5B7E29BD7E608E8025828F0E0185F32F90D741A5C67B9C8AEB65A33C65EBF0627A226D9A051FC0662DF1490AE4C22CC94B99776BF879B4B0F
INFORLIFE SA Gen POA.pdf	7F0F091EE32A2FC1C6BA698D96BCC0A6665E8E9C7F70A1F603E5212F4381CB8BE3F66C8D3B084295448BD70483B699BA3073EB7BEECDF4E15B465522C8BFC4FB
4830-114US2 Assignment.pdf	E1E34F1348AD79BF56AC144AC6EED80DF71A507ECFF169DF8D10944EC781B884B6FEFFA8BF4045C875110E89D74FE153CB3206D10E46B736070C3314AD11B0D8

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

ASSIGNMENT BY INVENTOR(S) OF PATENT APPLICATION FOR ALL COUNTRIES

BE IT KNOWN THAT, for good and valuable consideration paid to the undersigned inventor(s) (hereinafter ASSIGNOR(S)) by

Name: InfoRLife SA

Address: Casai, Campascio, Switzerland, 7748

(hereinafter ASSIGNEE),

the receipt and adequacy of which is hereby acknowledged, ASSIGNOR(s) hereby sell(s), assign(s) and transfer(s) to ASSIGNEE

all of his/her right, title and interest in, to and under the invention and application entitled:

READY-TO-USE KETAMINE PREMIX FORMULATION

for which application for Letters Patent of the United States ASSIGNOR(S) is/are the sole or a joint inventor and which application was executed on even date herewith or is identified as follows

U.S. Serial No.: 18/770,514 Filing Date: July 11, 2024

(Rothwell, Figg, Ernst & Manbeck is hereby authorized to insert the series code, serial or application number and/or filing date hereon, when known)

and all Letters Patent of the United States to be obtained on said application or on any continuation, division, reissue, reexamination or extension thereof and all rights connected therewith, and all applications for Letters Patent which may hereafter be filed for said invention in any country or countries foreign to the United States, and all Letters Patent which may be granted for said invention in any country or countries foreign to the United States and all extensions, renewals and reissues thereof and all rights of priority in any such country or countries based upon the filing of the said application for Letters Patent of the United States which are created by any law, treaty or international convention, for the full term or terms for which the same may be granted, including all rights to recover damages for any and all past infringement; and

ASSIGNOR(S) agree(s) to execute all papers necessary in connection with said application and any continuing, divisional, reissue or reexamination applications thereof and to execute separate assignments in connection with such applications as ASSIGNEE may deem necessary.

ASSIGNOR(S) agree(s) to execute all papers necessary in connection with any interference, litigation, or other legal proceeding which may be declared concerning this application or any continuation, division, reissue or reexamination thereof or Letters Patent, reissue patent or reexamination certificate issued thereon and to cooperate with ASSIGNEE in every way possible in obtaining and producing evidence and proceeding with such interference, litigation, or other legal proceeding.

ASSIGNOR(S) covenant(s) that he/she has the full right to convey the entire interest herein assigned and has not executed, and will not execute, any agreement in conflict herewith.

ASSIGNOR(S) acknowledge(s) that ASSIGNEE may appoint any attorney or practitioner of ASSIGNEE'S choice to prosecute any application or other legal proceeding involving said invention

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and ASSIGNOR(S) further acknowledge(s) that any attorney or practitioner so appointed by ASSIGNEE does not represent ASSIGNOR(S) and that such appointment by ASSIGNEE does not create any attorney-client relationship between ASSIGNOR(S) and any attorney or practitioner appointed by ASSIGNEE.

IN WITNESS WHEREOF, ASSIGNOR(S) has/ have affixed his/her signature below.

Signature:	Dated as of:
Typed Name: Sergio DUSCI	03/27/2024

WITNESSES: (optional)	
Signature:	Date:
Typed Name:	
Signature:	Date:
Typed Name:	

ACCEPTED AND ACKNOWLEDGED FOR AND ON BEHALF OF THE ASSIGNEE:	
Assignee Name:	InfoRLife SA
Signature of Authorized Person:	
Typed/Printed Name of Authorized Person:	
Title:	
Date:	

NO LEGALIZATION REQUIRED. THIS DOCUMENT MAY BE NOTARIZED IF DESIRED FOR FURTHER PROOF OF EXECUTION.

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PTO/AIA/80 (07-17)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 6449

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number

Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 6449

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: INFORLIFE SA
CASAI, CAMPASCIO SWITZERLAND 7748

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature Sergio Dusci Digitally signed by Sergio Dusci Date: 2024.07.12 10:17:43 +02'00'	Date 07/12/2024
Name Sergio Dusci	Telephone +41838192020
Title Managing Director	

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Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/770,514

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x =	0
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2820

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/770,514	07/11/2024		2820	4830-114US2	30	3

CONFIRMATION NO. 2594

FILING RECEIPT

6449
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

OC00000007559390

Date Mailed: 07/26/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Sergio DUSCI, Tresivio, ITALY;

Applicant(s)

INFORLIFE SA, CAMPASCIO, SWITZERLAND;

Assignment For Published Patent Application

INFORLIFE SA, CAMPASCIO, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 6449

Domestic Priority data as claimed by applicant

This appln claims benefit of 63/513,225 07/12/2023

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

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If Required, Foreign Filing License Granted: 07/24/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/770,514**

Projected Publication Date: 01/16/2025

Non-Publication Request: No

Early Publication Request: No
Title

READY-TO-USE KETAMINE PREMIX FORMULATION

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

Par Health Inc. Ex. 1002-0179

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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Par Health Inc. Ex. 1002-0180

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Kathi Vidal

Kathi Vidal
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Derrick Brent
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

Par Health Inc. Ex. 1002-0181

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 08/27/2024

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
08/27/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0182

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio	
	Examiner APRIL M WISE	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 11 July 2024 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to undersigned at (571)272-1642.

In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/APRIL M WISE/ Paralegal Specialist, Office of Petitions	

Par Health Inc. Ex. 1002-0183

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 09/17/2024

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/17/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Par Health Inc. Ex. 1002-0184

Office Action Summary	Application No. 18/770,514	Applicant(s) DUSCI, Sergio	
	Examiner SVETLANA M IVANOVA	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/11/2014.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 1-30 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Par Health Inc. Ex. 1002-0185

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions and

Notice of Non-Compliant Amendment

In the interest of compact prosecution the instant office action has been made simultaneously both an Election/Restrictions requirement and a Notice of Non-Compliant Amendment.

Regarding the Notice of Non-Compliant Amendment, the Examiner notes that the instant application was filed under the TRACK 1 program. This program has the following requirement under Section 2.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Sergio DUSCI	Nonprovisional Application Number (if known):	
Title of Invention:	READY-TO-USE KETAMINE PREMIX FORMULATION		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

Applicant's claim are non-compliant because they consist of 5 independent claims, in lieu of 4.

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine product is sterile and ready-to-use (RTU).

19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

26. A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.8 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

28. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

Appropriate correction is requested to bring down the number of independent claims to no more than four.

Regarding the Restriction/ Election requirement, Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-25, 29, and 30, drawn to:

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine product is sterile and ready-to-use (RTU).

19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.

29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

classified in classes A61K31/135, A61K45/06 and A61M5/14.

II. Claims 26 and 27, drawn to:

26. A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

classified in classes A61K31/135, A61K45/06 and A61M5/14.

III. Group III, claim 28, drawn to:

28. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

classified in classes A61K31/135, A61K45/06 and A61M5/14.

Inventions I and II, and I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h).

In the instant case the various ketamine products of Group I, can be used for purposes other than for: a method of preparing a ketamine product of Group I (Group II); or a method of treating a subject in need of analgesia (Group III). The various ketamine products claimed can be used in a materially different process of using that

product. On a related note, Applicant's attention is further directed to claim 26, which refers to the product of claim 1, but recites an infusion bag, where such an infusion bag is not recited in claim 1.

The ketamine products of Group I are directed to related products- i.e. a ketamine product, which is ready to use; a ketamine product, which is a ready to use infusion container; and a ketamine product, which is an infusion bag and is ready to use. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed can have a materially different design, mode of operation, function, or effect. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. In lieu of creating different groups for the various products, the Examiner has requested below that Applicant elect a species of a ketamine product, and to specifically designated the claims, which read on it.

Because the inventions of Groups I and II and I and III, are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02) due to their classification in different classes and subclasses. Accordingly, restriction for examination purposes as indicated is proper.

Restriction for examination purposes between the methods of Groups II and III, as indicated is proper because all these inventions listed in this action are independent

or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(A) **Separate classification thereof**: This shows that each invention has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Patents need not be cited to show separate classification.

(B) **A separate status in the art when they are classifiable together**: Even though they are classified together, each invention can be shown to have formed a separate subject for inventive effort when the examiner can show a recognition of separate inventive effort by inventors. Separate status in the art may be shown by citing patents which are evidence of such separate status, and also of a separate field of search.

(C) **A different field of search**: Where it is necessary to search for one of the inventions in a manner that is not likely to result in finding art pertinent to the other invention(s) (e.g., searching different classes/subclasses or electronic resources, or employing different search queries, a different field of search is shown, even though the two are classified together. The indicated different field of search must in fact be pertinent to the type of subject matter covered by the claims. Patents need not be cited to show different fields of search.

In the instant case, the method of Groups II and III require separate searches, and further have separate classification.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required

because the inventions require **a different field of search** (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Election of Species

This application contains claims directed to the following patentably distinct species:

If Group I is elected, the following species election is required:

a) Election of a single type of a ketamine product, i.e., a ketamine product, which is ready to use; a ketamine product, which is a ready to use infusion container; and a ketamine product, which is an infusion bag and is ready to use.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all claims are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement

may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

No telephone call was made due to the complexity of the restriction/ election requirement.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SVETLANA M IVANOVA whose telephone number is (571)270-3277. The examiner can normally be reached 8:30-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SVETLANA M IVANOVA/
Primary Examiner, Art Unit 1627

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**09/30/2024 01:22:41 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	67371610	FILING DATE	07/11/2024
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Aydin Harston

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-114US2 Response to RR.pdf	3	Response to Election / Restriction Filed	53 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
4830-114US2 Response to RR.pdf	D82C89B2C6DA7D864869DD6DB5EE98FFE8D6ECFFC9E3621F56A7BF404632445A057D703FEF859638C31812CF56FF70906FA77715F7C990C8787FA318B337C70C

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	18/770,514
First Named Inventor	:	Sergio DUSCI
Filed	:	July 11, 2024
Art Unit	:	1627
Examiner	:	SVETLANA M IVANOVA
Docket No.	:	4830-114US2
Customer No.	:	6449
Confirmation No.	:	2594

RESPONSE TO RESTRICTION AND
ELECTION OF SPECIES REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

In response to the Restriction and Election of Species Requirement mailed on September 17, 2024, please enter the following remarks and elections.

First, the Action states that there is a "Notice of Non-Compliant Amendment." The Office alleges that the application consists of 5 independent claims and lists claims 1, 19, 26, 28, and 29 as allegedly being independent. This is incorrect. It appears that the Office has overlooked the fact that claims 26 and 28 are clearly dependent on claim 1 as bolded below:

26. A method of preparing the ketamine product **of claim 1**, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

28. A method of treating a subject in need of analgesia, comprising administering the ketamine product **of claim 1** to the subject as a continuous infusion.

This application only contains 3 independent claims (1, 19, and 29). The Office has already acknowledged this fact by not charging any excess claims fees for more than 3 independent claims. See PTO form "Patent Application Fee Determination Record" issued on July 26, 2024 that is in the file wrapper for this application and the relevant portion is captioned below:

PATENT APPLICATION FEE DETERMINATIO

Substitute for Form PTO-875

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)
FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))		

* If the difference in column 1 is less than zero, enter "0" in column 2.

Thus, Applicant respectfully requests that the Notice of Non-Compliant Amendment be rescinded.

In response to the Restriction Requirement, Applicant hereby **elects Group I, claims 1-25, 29, and 30.**

In response to the Election of Species Requirement, Applicant hereby **elects a ketamine product, which is ready to use.** This generic term "product" includes any type of product including containers and bags.

Claims 1-30 read on the elected species.

Early and favorable action on the merits of this application is respectfully requested.

Par Health Inc. Ex. 1002-0199

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Applicant believes that this response is timely filed. However, if any fees are necessary, authorization is hereby given to charge Deposit Account No. 02-2135; please credit any overpayment.

Respectfully submitted,

By: /Aydin H. Harston/

Aydin H. Harston, Ph.D.
Attorney for Applicant
Registration No. 65249
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W., Suite 900 East
Washington, D.C. 20001
Telephone: (202) 783-6040

Par Health Inc. Ex. 1002-0200

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 10/08/2024

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/08/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0201

Examiner-Initiated Interview Summary	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio		
	Examiner SVETLANA M IVANOVA	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
SVETLANA M IVANOVA	Primary Examiner	Telephonic
AYDIN H. HARSTON	Attorney of Record	

Date of Interview: 03 October 2024

Issues Discussed:

Other

The Examiner called Applicant's attorney on 10/2/2024, pursuant to Applicant's filing of a response on 9/30/2024 requesting that the notice of non-compliant amendment be rescinded on grounds that the office has already acknowledged the fact the fact that there are only three independent claims (claims 1, 19 and 29) by not charging any excess claim fees. The Examiner noted in her voice mail that claims 26 and 28, although written as dependent on product claim 1, recite different statutory categories of invention (a process of making, and a method of treating, respectively), and that such claims are normally written in independent claim format. She asked that Applicant call her back to advise how it wishes to proceed. Applicant instead called the Examiner's SPE Kortney Klinkel and asked that she explain to the Examiner that these are dependent claims. The Examiner's SPE contacted the Examiner on 10/3/2024 to ask her to call Applicant and advise that the notice of non-compliant amendment will be withdrawn, and that the independent claims are only 3. The Examiner called Applicant back, and she noted that the claims are different statutory categories of invention, which were thus properly restricted as independent and distinct, but that on further checking she will have to agree that claims 26 and 28 will have to be treated as proper dependent claims. Specifically, the Examiner has checked MPEP 608.01(n).III (Test for proper dependency), and per it, will have to agree that these claims will have to be treated as proper dependent claims.

“The fact that the independent and dependent claims are in different statutory classes does not, in itself, render the latter improper. Thus, if claim 1 recites a specific product, a claim for the method of making the product of claim 1 in a particular manner would be a proper dependent claim since it further specifies limitations relating to the method of making the product of claim 1. Similarly, if claim 1 recites a method of making a product, a claim for a product made by the method of claim 1 could be a proper dependent claim. On the other hand, if claim 1 recites a method of making a specified product, a claim to the product set forth in claim 1 would not be a proper dependent claim if the product can be made by a method other than that recited in the base method claim, and thus, does not include the limitations of the base claim. “

Par Health Inc. Ex. 1002-0202

Examiner-Initiated Interview Summary	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio		
	Examiner SVETLANA M IVANOVA	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** **2 of 2**

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Par Health Inc. Ex. 1002-0203

Notice of References Cited	Application/Control No. 18/770,514	Applicant(s)/Patent Under Reexamination DUSCI, Sergio	
	Examiner SVETLANA M IVANOVA	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-11207309-B2	2021-12-28	Conrad; Andrew	A61K31/4468	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Par Health Inc. Ex. 1002-0204

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

CPC - Searched*		
Symbol	Date	Examiner
A61K31/135	10/18/2024	si

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Filing receipt review	10/18/2024	si
DAV inventor search	10/18/2024	si
PE2E assignee search	10/18/2024	si
PE2E (attached)	10/18/2024	si
Google (attached)	10/18/2024	si

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Par Health Inc. Ex. 1002-0265

Bibliographic Data

Application No: 18/770,514

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /SVETLANA M IVANOVA/ (Examiner's Signature) | si (Initials)

Title: READY-TO-USE KETAMINE PREMIX FORMULATION

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/11/2024	514	1627	
RULE			

APPLICANTS

INFORLIFE SA, CAMPASCIO, SWITZERLAND

INVENTORS

Sergio DUSCI, Campascio, SWITZERLAND

CONTINUING DATA

This application has PRO of 63513225 07/12/2023

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

07/24/2024

STATE OR COUNTRY

SWITZERLAND

ADDRESS

FILING FEE RECEIVED

$7,160

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	40	"5439643"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:16 PM
L2	19	"8617467"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:21 PM
L3	75006	A61K31/135	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:24 PM
L4	45591	A61K31/135.ipcr,cpc.	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:24 PM
L5	17	"11207309"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/17 10:11 PM
L6	4	((("INFORLIFE") near3 ("SA"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:28 PM
L7	331	(ketamine AND (solution OR aqueous)).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM
L8	438397	infusion	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM
L9	104	L7 AND L8	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
10/17/2024 12:56:00 PM	Google	ketamine infusion
10/17/2024 5:22:27 PM	Google	ketalar label
10/17/2024 5:22:42 PM	Google	ketalar label par pharmaceutical
10/17/2024 7:07:09 PM	Google	polycine APP-114S polyelite EHC film bag
10/17/2024 7:58:15 PM	Google	polycine APP-114S polycine
10/17/2024 10:22:27 PM	Google	Polyolefin based APP- 114-S
10/17/2024 10:39:46 PM	Google	Polyolefine APP-114-S polycine
10/17/2024 10:51:16 PM	Google	polyolefine app-114-s polycine product data sheet
10/17/2024 10:56:35 PM	Google	APP114-S polycine
10/17/2024 11:37:04 PM	Google	climaprop II
10/17/2024 11:40:05 PM	Google	Us 11207309 b2
10/17/2024 11:41:40 PM	Google	Film 140 MM Width × 265 MM, Climaprop II (12PET/9ALU/80PE)
10/17/2024 11:59:42 PM	Google	TP823 closure
10/18/2024 12:00:34 AM	Google	TP823 stopper

Par Health Inc. Ex. 1002-0208

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Sergio DUSCI
Art Unit	
Examiner Name	
Attorney Docket Number	4830-114US2

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5439643	A	1995-08-08	LIEBERT	
	2	8617467	B2	2013-12-31	RODRIGUEZ ET AL	

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	1							☐

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Par Health Inc. Ex. 1002-0209

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Sergio DUSCI
	Art Unit	
	Examiner Name	
	Attorney Docket Number	4830-114US2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Ketamine Hydrochloride-ketamine hydrochloride injection, solution, concentrate, Hospira-ANDA 074549, 2022 (23 pages)	☐
	2	Ketamine Hydrochloride-ketamine hydrochloride injection, Hikma-ANDA 074524, 2022 (20 pages)	☐
	3	Ketamine Hydrochloride-ketamine hydrochloride injection, AuroMedics-ANDA 076092, 2022 (28 pages)	☐
	4	Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, 2022 (13 pages)	☐
	5	<785> OSMOLALITY AND OSMOLARITY, (http://www.uspbpep.com/usp31/v31261/usp31nf26s1_c785.asp), Pharmacopeial Forum : Volume No. 34(1), 2024 (3 pages)	☐
	6	<1222> Terminally Sterilized Pharmaceutical Products—Parametric Release, (https://www.uspnf.com/purchase-usp-nf#:~:text=The%20current%20version%20of%20USP,official%20on%20May%201%2C%202024), United States Pharmacopeia (2024). (7 pages)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/SVETLANA M IVANOVA/	Date Considered	10/16/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Par Health Inc. Ex. 1002-0210

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Sergio DUSCI
	Art Unit	
	Examiner Name	
	Attorney Docket Number	4830-114US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Aydin H. Harston/	Date (YYYY-MM-DD)	2024-07-11
Name/Print	Aydin H. Harston, Ph.D.	Registration Number	65,249

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Par Health Inc. Ex. 1002-0211

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 10/23/2024

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/23/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0213

Office Action Summary	Application No. 18/770,514	Applicant(s) DUSCI, Sergio	
	Examiner SVETLANA M IVANOVA	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/30/2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) 26-28 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-25 and 29-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Par Health Inc. Ex. 1002-0214

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

Applicant's response to the restriction/ election requirement from 8/30/3034 is acknowledged. Applicant has made the following election.

> In response to the Restriction Requirement, Applicant hereby **elects Group I, claims 1-25, 29, and 30.**
>
> In response to the Election of Species Requirement, Applicant hereby **elects a ketamine product, which is ready to use.** This generic term "product" includes any type of product including containers and bags.
>
> Claims 1-30 read on the elected species.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)). The restriction/ election requirement is hereby MADE FINAL. Claims 1-25, 29 and 30 are pending, and have been examined herewith.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8, 18-25, 29 and 30 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record), or in the alternative under 35 U.S.C. 103 as being unpatentable over Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record).

Ketalar is an FDA label for ketamine hydrochloride injection. Ketalar discloses preparing a Ketalar product/ (vial or for infusion) for induction of anesthesia by diluting Ketalar with sterile water for injection, USP, normal saline, USP, and dextrose in water. For maintenance of anesthesia, it discloses: "To prepare a dilute solution containing 1 mg of ketamine per mL, aseptically transfer 10 mL from a 50 mg per mL vial or 5 mL from a 100 mg per mL vial to 500 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (Normal Saline) and mix well. The resultant solution will contain 1 mg of ketamine per mL Use immediately after dilution. When fluid restriction is required, KETALAR can be added to a 250 mL infusion as described above to provide a KETALAR concentration of 2 mg/mL." (p. 3). Ketalar is diluted in sterile water. (*Id.*). Ketalar states that ketamine hydrochloride is formulated as slightly acidic (pH 3.5-5.5).

Further regarding infusion, Ketalar discloses that Ketalar should be given by slow microdrip infusion technique at a dose of 0.1 to 0.5 mg/ minute to maintain general anesthesia. (p. 3). To one of skill in the art, this description, and the above description

of addition to the ketamine product a 250 mL infusion, indicates by the use of an infusion container/ bag.

Since Ketalar discloses a product with the same ingredients, it will also have the same osmolality, as per Applicant's claim 8, the same shelf life, as per Applicant's claims 21 and 22, the same chemical stability, as per Applicant's claim 23, the same average number of particles following storage of the ketamine product, as per Applicant's claim 24, the same ketamine content after accelerated storage, as per Applicant's claim 25, and the same shelf-life, as per Applicant's claim 30.

Applicant's claim 1 recites that the ketamine product is ready-to-use (RTU). It is noted that the broadest reasonable interpretation of this claim term does include a RTU product as prepared in the description above, i.e. one which is pre-mixed and prepared for immediate use after dilution. This BRI renders Applicant's claims anticipated.

Even if RTU is interpreted to mean pre-mixed, pre-diluted, it would have been obvious to a person of skill in the art before the effective filing date of the claimed invention, based on the disclosure of Ketalar, to prepare such a product with a reasonable expectation of success. Ketaler essentially teaches this product made just prior administration, based on which it would have been obvious to the skilled artisan to also prepare the pre-diluted product as well guided by considerations of ease of administration. Ketalar further renders obvious Applicant's claim 18, 19 and 29- that the ketamine product is autoclaved, and that the infusion container/ bag is terminally sterilized, or that the ketamine product is aseptically filled, since it teaches that the Ketaler product is USP grade and sterile, sterility of a product is a known function of

autoclaving to one of skill in the art, and FDA approved injections/ infusions for *in vivo* administration in humans are for sterile/ aseptic products.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7 and 9-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record), as applied to claims 1-6, 8, 18-25, 29 and 30 in the 35 U.S.C. 103 rejection above, and further in view of US 11,207,309 B2 to Conrad et al. ("Conrad").

Ketalar is discussed in the 35 U.S.C. 103 rejection above.

Ketalar discloses administration by infusion, but does not specifically disclose the characteristics of the infusion container/ bag of Applicant's claims 7 and 9-17.

For starters, it is noted that what is disclosed as subject matter in these claims, even per Applicant's own specification is in fact commercially available infusion bags.

[00047] In one aspect, the intravenous bag is made up of multilayer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer.

Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

> infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation; an M315 film manufactured by SealedAir Corporation; an APP-series film manufactured by Polycine, such as APP-114S film manufactured by Polycine; a polypropylene film, such as those manufactured by Technoflex, such as an Inerta® film manufactured by Technoflex; a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa; an Inerta 103 film, made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer, which may be manufactured by Technoflex; or another commercially-available polymer film designed for use in intravenous bag products. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the infusion bag.
>
> **[00054]** In certain aspects, the infusion container (e.g., infusion bag) is contained in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

Conrad relates to parenteral liquid formulations of fentanyl, which are stable formulations supplied as a ready-to-administer product in an infusion container or bag. The stable formulations are terminally sterilized in the infusion container. (Abstract). Conrad further discloses wherein the formulation is stored in an infusion container and

terminally sterilized, for example, by autoclaving. Conrad specifically discloses an infusion bag, per Applicant's claims.

TABLE 7

Component	Description
IV bag and tube	100 cc: Polycine APP114 multilayer polyolefin/ styrene block copolymer, 200 µm Tube: APP107, 1000 µm 250 cc: Polycine APP114 multilayer polyolefin/ styrene block copolymer, 200 µm Tube: APP107, 1000 µm
Twist-off stopper	Polypropylene twist-off, TP823
Overwrap	Film 140 MM Width × 265 MM, Climaprop II (12PET/9ALU/80PE) Film 140 MM Width × 290 MM, Climaprop II (12PET/9ALU/80PE)

Conrad further discloses a twist-off closure with the characteristics of Applicant's claim 11. "The formulations of the present invention can be filled in an infusion containing a head space. Storing injectable solutions in containers generally requires an inert head space (e.g., nitrogen or argon) to reduce the loss of stability. The fentanyl formulations can be filled into infusion containers by conventional methods without the need for filling under inert gas and purging of the head space to eliminate the presence of oxygen, for example, below 5 percent. As such, the fentanyl formulations can be utilized with a broad range of filling procedures without the need for modifying equipment or operating procedures to accommodate for inert gas filing conditions." (col. 11, ll. 14-26). "Containers are sealed as typical in the industry, for example, with the use of a lid, cap, closure and the like. Polymeric bags such as those manufactured by Technoflex and Polycine." (col. 8, l. 67-col. 9, l. 3).

Per Conrad, the polymeric infusion bag can have an aluminum overpouch. Per Conrad, example materials for the containers and container components can include polyolefins, polysulfone, polycarbonate, polypropylene, polyethylene (LDPE or HDPE), ethylene/propylene copolymers, acrylic-imide copolymers, polyester (e.g. PET, PEN and the like), Teflon, Nylon, acetal (Delrin), polymethylpentene, PVDC, ethylvinylacetate, AN-copolymer or polyioprene. Preferably, the materials for the container and container components are suitable to withstand aseptic filling and not deform during terminal sterilization. (col. 6, ll. 40-56).

Even though Conrad does not specifically disclose that the infusion bag is 3-layers, and that the overwrap 4-layers, as can be seen from the above disclosure, Conrad specifically discloses that the infusion bag is multilayer, that the overwrap is at least two layers and that an additional layer is one of aluminum, as well as names other possible layers with polyester, polypropylene, etc.

Accordingly, it would have been obvious to a person of skill in the art before the effective filing date of the claimed invention to modify the teachings of Ketalar and Conrad in order to practice Applicant's claimed invention with a reasonable expectation of success. The skilled artisan would have been motivated to do so, because Ketalar teaches preparing a RTU ketamine product as an infusion, and Conrad discloses that infusion bags/ containers of different kinds, to include the specific one claimed in Applicant's claims, are readily commercially available in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SVETLANA M IVANOVA whose telephone number is (571)270-3277. The examiner can normally be reached 8:30-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197

(toll-free). If you would like assistance from a USPTO Customer Service

Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SVETLANA M IVANOVA/
Primary Examiner, Art Unit 1627

PTO/SB/08a (01-22)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

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Par Health Inc. Ex. 1002-0225

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18770514
	Filing Date	2024-07-11
	First Named Inventor	Sergio DUSCI
	Art Unit	1627
	Examiner Name	SVETLANA M IVANOVA
	Attorney Docket Number	4830-114US2

	1	Department of Health and Human Services, FDA-2022-D-0219, Human Prescription Drug and Biological Products-Labeling for Dosing Based on Weight or Body Surface Area for Ready-to-Use Containers-"Dose Banding", Guidance for Industry, pp. 2-3 (2023); (10 pages).	☐
	2	"An Overview of Compounding", in 2; National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy: A Review of Safety, Effectiveness, and Use.; National Academies Press; July 1, 2020; (10 pages).	☐
	3	"Parenteral Preparations: Formulation Challenges"; Manufacturing Chemist, February 6, 2017; https://www.manufacturingchemist.com/news/article_page/Parenteral_preparations_formulation_challenges/125615; (8 pages).	☐
	4	N.P. SHAH, et al.; "Do You Know the Difference Between Extractables and Leachables?"; Azenta Life Sciences; July 10, 2019; https://www.azenta.com/blog/do-you-know-difference-between-extractables-and-leachables; (6 pages).	☐
	5	T. Ofenböck; "Terminal Sterilisation of Parenteral Drugs"; Process Tech. Online; February 18, 2022; https://process-technology-online.com/pharma/terminal-sterilisation-of-parenteral-drugs/; (5 pages).	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Par Health Inc. Ex. 1002-0226

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2024-11-22
Name/Print	Sheena X. Wang	Registration Number	82,893

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Par Health Inc. Ex. 1002-0227

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**11/25/2024 09:56:55 AM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Giovanelly Castell
PATENT CENTER #	68095618	FILING DATE	07/11/2024
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Sheena Wang

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-114US2-Amendment_in_response_to_10-23-24_OA.pdf	15	Amendment/Request for Reconsideration-After Non-Final Rejection	82 KB
4830-114US2-IDS-SB08.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1314 KB
4830-114US2-SHAH_Ref.pdf	6	Non Patent Literature	2257 KB
4830-114US2-Parenteral-Preparations.pdf	8	Non Patent Literature	3064 KB
4830-114US2-Dose-Banding_Ref.pdf	10	Non Patent Literature	3341 KB
4830-114US2-Overiew_Compounding_Ref.pdf	10	Non Patent Literature	4979 KB

4830-114US2-Ofenbock_Ref.pdf	5	Non Patent Literature	1483 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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4830-114US2-Dose-Banding_Ref.pdf	2B07CFCA1585E46C6BAA3E6AD75B5DDEAFDE4E21B53AC1709D1CEEF96D5F22CA044029673E302A09268D943C83B7BD3B2D27D4EA14923127FCC52B71F49EE2A3
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4830-114US2-Ofenbock_Ref.pdf	1BD365CCDE007965B18A658F18B5AA853FF24EC21E572E67B0F634B8F358E8BB05677FC9A29281094F4B496B3873127300D1BB3514FCC39FA16EDFDD84253CF7

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security

and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**11/25/2024 09:56:55 AM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Giovanelly Castell
PATENT CENTER #	68095618	AUTHORIZED BY	Sheena Wang
CUSTOMER #	6449	FILING DATE	07/11/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Sergio DUSCI

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 022135	**E2024AO057088805**	**Giovanelly Castell**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
			TOTAL AMOUNT:	**$260.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	: 18/770,514
1ST NAMED INVENTOR	: Sergio DUSCI
FILED	: July 11, 2024
ART UNIT	: 1627
EXAMINER	: SVETLANA M IVANOVA
CONFIRMATION NO.	: 2594
DOCKET NO.	: 4830-114US2
CUSTOMER NO.	: 6449

REPLY TO NON-FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated October 23, 2024, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine product is sterile and ready-to-use (RTU) wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.
2. (Original) The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.
3. (Original) The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.
5. (Original) The ketamine product of claim 1, wherein the ketamine solution is free of benzethonium chloride.
6. (Original) The ketamine product of claim 1, wherein the pH of the aqueous ketamine solution is about 3 to about 6.
7. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
8. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
9. (Original) The ketamine product of claim 7, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
10. (Original) The ketamine product of claim 7, wherein the closure comprises a plastic material.
11. (Original) The ketamine product of claim 7, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts,

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wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

12. (Original) The ketamine product of claim 10, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

13. (Currently Amended) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of ~~polyolefin,~~ polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

14. (Original) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

15. (Currently Amended) The ketamine product of claim 7, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises ~~comprising~~ polypropylene styrene-block copolymer.

16. (Original) The ketamine product of claim 7, wherein the infusion bag is contained within an overwrap.

17. (Original) The ketamine product of claim 16, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

18. (Original) The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

19. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

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20. (Original) The ketamine product of claim 19, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

21. (Cancelled).

22. (Cancelled).

23. (Original) The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

24. (Original) The ketamine product of claim 1, wherein the average number of particles equal to or greater than 10 µm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months; and/or

the average number of particles equal to or greater than 25 µm does not exceed 600 per container following storage of the ketamine product at room temperature for 24 months.

25. (Currently Amended) The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than [[99%]] 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is [[99%]] 97% or greater compared to the ketamine content before storage.

26. (Withdrawn) A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

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27. (Withdrawn) The method of claim 26, wherein the step of terminally sterilizing comprises autoclaving the infusion bag at a temperature between about 110 to about 130° C for a period of time of about 7 to about 60 minutes.

28. (Withdrawn) A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

29. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU), wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

30. (Cancelled).

31. (New) The ketamine product of claim 19, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

32. (New) The ketamine product of claim 29, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

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REMARKS/ARGUMENTS

Claims 1-20, 23-29, and 31-32 are pending. Claims 1, 13, 15, 19, 25 and 29 are amended and new claims 31-32 are added. Claims 21, 22 and 30 are cancelled. Claims 26-28 are withdrawn from consideration. Claims 13 and 15 are amended to improve clarity. Support for all amendments is found throughout the specification as filed and original claims, including, *inter alia*, original claims 21, 22 and 30; and paragraphs [0021], [0024], [0058], [0061], [0063], [0065], [0100], [0112]-[114], and tables 6-9 of the specification. A total of 29 claims are pending. No new matter has been added.

The Applicant has not publicly dedicated or abandoned any unclaimed subject matter or acquiesced to any objection or rejection set forth in the Office Action. The Applicant expressly reserves the right to pursue prosecution of any presently or previously unelected, excluded, or cancelled claim embodiments, and/or species in one or more future continuation and/or divisional applications.

In response to the Office Action, favorable reconsideration and allowance of the present application are respectfully requested.

For the reasons discussed below, it is submitted that this application is in condition for allowance.

Response to Claim Rejections – 35 U.S.C. § 102(a)(1) or 35 U.S.C. § 103 Based on NDA016812 ("Ketalar")

Claims 1-6, 8, 18-25, 29 and 30 are rejected under 35 U.S.C. § 102(a)(1) as allegedly being anticipated by Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar"); or in the alternative under 35 U.S.C. § 103 as being unpatentable over Ketalar. Ketalar discloses preparing a ketamine product (vial or for

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infusion) for induction of anesthesia by diluting Ketalar with sterile water for injection, USP, normal saline, USP, or dextrose in water. The Office Action acknowledges that **Ketalar requires dilution prior to use**. O.A. at p. 3-4. Furthermore, the Office Action acknowledges that the **Ketalar product needs to be used immediately after dilution**. *Id.*

Applicant traverses this rejection because the cited art, considered alone or in combination, does not teach and would not have suggested all of the features of amended claims 1, 19 and 29. "To reject a claim as anticipated by a reference, the disclosure must teach every element required by the claim under its broadest reasonable interpretation." MPEP § 2131. Furthermore, the MPEP also requires the "consideration" of every claim feature in an obviousness determination. MPEP § 2143.03. To render independent claims 1, 19 and 29 unpatentable, Ketalar must **teach or suggest each and every claim feature**. *See In re Royka*, 490 F.2d 981 (CCPA 1974).

On page 4 of the Office Action, the Office asserts that "the broadest reasonable interpretation of this claim term [ready-to-use] does include a RTU product as prepared in the description above, i.e. one which is pre-mixed and prepared for immediate use after dilution. This BRI renders Applicant's claims anticipated." Applicant respectfully disagrees. The specification defines the term "ready-to-use" or "ready to use" as referring to "premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration." (Paragraph [0075].) A person of ordinary skill in the art would not interpret the term "ready-to-use" to include a drug product that requires dilution immediately prior to use. A "ready-to-use" drug product is a term of art meaning "a drug product… from

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which the entire drug content of the container(s) is administered to the patient," which "may simplify the preparation and administration of a drug compared to preparing and administering an exact weight- or BSA-based dose to the patient." DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA-2022-D-0219, HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS-LABELING FOR DOSING BASED ON WEIGHT OR BODY SURFACE AREA FOR READY-TO-USE CONTAINERS-"DOSE BANDING"; GUIDANCE FOR INDUSTRY, at 2-3 (2023).

A person of ordinary skill would recognize that Ketalar is not, and does not suggest, a **sterile, ready-to-use** ketamine product comprising from 0.5 to about 2.5 mg/mL ketamine; Ketalar is a concentrated product that must be manipulated to transfer it to an infusion container and diluted to an appropriate concentration—those steps compromise sterility and mean that the product Ketalar product is not "ready-to-use." Those steps must be completed by a medical professional at the point of administration or by a compounding pharmacy, creating the risk of errors and/or contamination. *See* National Academies of Sciences, Engineering, and Medicine, *An Overview of Compounding*, in 2 THE CLINICAL UTILITY OF COMPOUNDED BIOIDENTICAL HORMONE THERAPY: A REVIEW OF SAFETY, EFFECTIVENESS, AND USE, 2 (Jul. 1, 2020) ("Compounded drugs should only be used in patients whose medical needs cannot be met by an FDA-approved drug. Unnecessary use of compounded drugs may expose patients to potentially serious health risks. For example, poor compounding practices can result in serious drug quality problems, such as contamination or a drug that contains too much or too little active ingredient. This can lead to serious patient injury and death.").

Nevertheless, Applicant has amended independent claims 1, 19, and 29 to further recite that the claimed sterile, RTU ketamine product "<u>has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C</u>." As indicated above, the Office

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Action acknowledges that Ketalar does not teach a ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine wherein the ketamine product is sterile and has a shelf life of more than six months when stored at controlled room temperature. O.A. at p. 3-4. Rather, Ketalar teaches that the Ketalar product is supplied and stored at 10 mg/mL, 50 mg/mL or 100 mg/mL in a "multiple dose vial;" its "dosage must be individualized and titrated to the desired clinical effect;" and must be "**[u]se[d] immediately after dilution**." Ketalar at 1-4.

It would not have been obvious to a person of ordinary skill to prepare sterile, a ready-to use ketamine drug product with at least six month shelf-life at room temperature with a reasonable expectation of success. The shelf-life of pharmaceutical products can be affected by the concentration of the active pharmaceutical ingredient, the excipients in the formulation and their concentrations, and the container in which the formulation is stored, among other things. *See Parenteral Preparations: Formulation Challenges*, MFG. CHEMIST (Feb. 6, 2017), https://www.manufacturingchemist.com/news/article_page/Parenteral_preparations_formulation_challenges/125615 ("The main challenge with parenteral dosage forms is achieving drug substance and excipient compatibility (that is, eliminating the formation of impurities by degradation of the drug substance or the formation of a new chemical entity between the drug substance and the excipients) as well as avoiding leaching/adsorption issues between the preparation and the primary container."); *Do You Know the Difference Between Extractables and Leachables?*, AZENTA LIFE SCI. (July 10, 2019), https://www.azenta.com/blog/do-you-know-difference-between-extractables-andleachables. Further, processes used to sterilize the finished product, including heat- or steam-based terminal sterilization processes, can promote degradation of the active pharmaceutical ingredient, excipients, and/or the container, including in ways that are unpredictable and specific to the identity and combination of ingredients and the container

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system. *See Parenteral Preparations, supra*; *see also* Ofenböck, Thomas, *Terminal Sterilisation of Parenteral Drugs*, PROCESS TECH. ONLINE (Feb. 18, 2022), https://process-technology-online.com/pharma/terminal-sterilisation-of-parenteral-drugs/.

Ketalar does not provide a person of ordinary skill with any guidance, suggestion, or motivation to prepare a **sterile, diluted** ketamine composition that can be stored for at least six months when stored at a controlled room temperature between 15–30°C. In fact, Ketalar repeatedly notes that the diluted ketamine solution must immediately be administered to the subject and is **not** suitable for prolonged storage.

The Office provides no basis or evidence to suggest that a person of ordinary skill in the art would have reasonably expected success in preparing a sterile, diluted product suitable for storage for at least six months when stored at a controlled room temperature as claimed.

Applicant also submits that the claimed ready to use premix composition provides for surprising and unexpected advantages over the concentrated compositions in the cited art. For example, the claimed ready-to-use composition provides advantages in the ability for the formulation to withstand terminal sterilization in a container suitable for direct administration to a patient and to store the composition over prolonged periods of time while maintaining stability at low, ready-to-use concentrations of ketamine **without** the benzethonium chloride preservative used in Ketalar. Such advantages over the concentrated multiple-dose vial compositions of the cited references are further evidence of the non-obviousness of the claims over the cited references. *See* M.P.E.P. § 716.02(a). For example, as described by the present application in paragraph 114, the claimed formulation "surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride

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under accelerated conditions and long-term storage." The ability to store the claimed composition for prolonged periods of time are shown in at least Examples 2 and 3 of the application, which demonstrate that a ready to use 1 mg/mL ketamine composition was stable after terminal sterilization and after 12 months when stored in an infusion bag having specific characteristics.

Thus, the prior art does not teach all of the elements of the claimed invention. Indeed, the prior art specifically teaches away from storing a diluted ketamine solution in room temperature for prolonged periods (e.g., at least six months as required by all pending claims, or twenty-four months as recited in dependent claims 23, 31, and 32). Furthermore, Applicant respectfully submits that the disclosures in Ketalar fail to provide reasonable guidance that would have motivated a skilled artisan to modify Ketalar, as alleged, with a reasonable expectation of success to achieve the claimed invention. Thus, the present invention is not obvious from the teachings of Ketalar.

All remaining claims under consideration (claims 2-20, 23-25, and 31-32) are dependent from one of claims 1, 19, or 29, and are therefore nonobvious for the same reasons. Therefore, Applicant respectfully requests that the rejections be withdrawn for at least these reasons. Claims 21-22 and 30 have been cancelled by the present amendment.

Response to Claim Rejections – 35 U.S.C. § 103 Based on Ketalar and Conrad

Claims 7 and 9-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ketalar further in view of US 11,207,309 B2 to Conrad *et al.* ("Conrad"). The Office notes that Ketalar is discussed in the above section and acknowledges that it does not disclose the characteristics of the infusion bag of claims 7 and 9-17. O.A. at p. 5. The Office further acknowledges that Conrad relates to parenteral liquid formulations of **fentanyl**. O.A. at p. 7. However, the Office notes that

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this fentanyl product is supplied as a terminally sterilized ready-to-administer product in an infusion container that has the characteristics of claims 7 and 9-17, including the twist-off closure and aluminum overpouch. *Id.* at 8-9.

First, the arguments outlined above with regard to claim 1 apply also to claims 7 and 9-17, which depend from claim 1. "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." 37 C.F.R. § 1.75. Therefore, claims 7 and 9-17 are non-obvious over Ketalar for the same reasons as discussed in the section above. Conrad fails to remedy the deficiencies of Ketalar because it does not teach or suggest a sterile, RTU ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, which can be stored for more than three months when stored at a controlled room temperature between 15–30°C.

Second, the Office alleges that one would combine Ketalar with Conrad because "because Ketalar teaches preparing a RTU ketamine product as an infusion, and Conrad discloses that infusion bags/ containers of different kinds, to include the specific one claimed in Applicant's claims, are readily commercially available in the art." *Id.* at 9. However, fentanyl and ketamine are different drug substances with different chemical properties, which may exhibit different sensitivities and different interactions with container materials. *See Parenteral Preparations: Formulation Challenges*, MFG. CHEMIST (Feb. 6, 2017), https://www.manufacturingchemist.com/news/article_page/Parenteral_preparations_formulation_challenges/125615; *Do You Know the Difference Between Extractables and Leachables?*, AZENTA LIFE SCI. (July 10, 2019), https://www.azenta.com/blog/do-you-know-difference-between-extractables-andleachables.

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"To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353, 1359 (Fed. Cir. 2008) (quoting *KSR,* 550 U.S. at 420). Furthermore, as the Office Action acknowledges on page 8-10, Conrad suggests that its fentanyl formulation can be contained in "infusion bags/containers of different kinds" including "[p]olymeric bags such as those manufactured by Technoflex and Polycine." Thus, Conrad provides no suggestion or disclosure that storage in the infusion bag having the properties of claims 7 and 9-17 provides for any advantages over storage in other containers. In contrast, as described above and shown in Examples 2 and 3 and Paragraph 121 of the specification, the ready-to-use ketamine formulations of the present application exhibited surprising and unexpected advantages with regard to stability when stored in an infusion bag having the properties of claims 7 and 9-17.

Thus, at least because the cited references do not disclose all of the elements of the claims, including that a ketamine composition comprising about 0.5 to about 2.5 mg/mL ketamine is stable for more than three months when stored an infusion bag having the properties disclosed in claims 7 and 9-17, the burden to establish a *prima facie* case of obviousness has not been carried. In addition, and as an independent basis to withdraw the rejection, because there was no showing that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR,* 550 U.S. at 416. Moreover, the Office has failed to establish a reasonable expectation of success that a person of ordinary skill would have had a reasonable expectation that the claimed **ketamine** composition would be stable for at least six months when

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stored at a controlled room temperature between 15–30°C when stored in one of the multiple the infusion bag options disclosed in Conrad.

Therefore, Applicant respectfully requests that the rejections of claims 7 and 9-17 be withdrawn, for at least these reasons as well.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections, and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

If any fees are required, such as, but not limited to, any extension of time fee under 37 C.F.R. 1.17, Applicant hereby petitions for an extension of time, if necessary, and authorizes the Office to charge all required fees to deposit account number 02-2135.

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Respectfully submitted,

By: /Sheena X. Wang/

Sheena X. Wang
Attorney for Applicant
Registration No. 82,893
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.,
Suite 900 East
Washington, D.C. 20001
Telephone: (202) 783-6040
Facsimile: (202) 783-6031

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

CPC - Searched*		
Symbol	Date	Examiner
A61K31/135	10/18/2024	si

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Filing receipt review	10/18/2024	si
DAV inventor search	10/18/2024	si
PE2E assignee search	10/18/2024	si
PE2E (attached)	10/18/2024	si
Google (attached)	10/18/2024	si
PE2E (ketamine and (aqueous or solution)).clm.	12/13/2024	si
Google (ketalar, ketamine, ready to use)	12/13/2024	si

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L10	332	(ketamine AND (solution OR aqueous)).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/12/13 09:45 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

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Par Health Inc. Ex. 1002-0252

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18770514
	Filing Date	2024-07-11
	First Named Inventor	Sergio DUSCI
	Art Unit	1627
	Examiner Name	SVETLANA M IVANOVA
	Attorney Docket Number	4830-114US2

	1	Department of Health and Human Services, FDA-2022-D-0219, Human Prescription Drug and Biological Products-Labeling for Dosing Based on Weight or Body Surface Area for Ready-to-Use Containers-"Dose Banding", Guidance for Industry, pp. 2-3 (2023); (10 pages).	☐
	2	"An Overview of Compounding", in 2; National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy: A Review of Safety, Effectiveness, and Use.; National Academies Press; July 1, 2020; (10 pages).	☐
	3	"Parenteral Preparations: Formulation Challenges"; Manufacturing Chemist, February 6, 2017; https://www.manufacturingchemist.com/news/article_page/Parenteral_preparations_formulation_challenges/125615; (8 pages).	☐
	4	N.P. SHAH, et al.; "Do You Know the Difference Between Extractables and Leachables?"; Azenta Life Sciences; July 10, 2019; https://www.azenta.com/blog/do-you-know-difference-between-extractables-and-leachables; (6 pages).	☐
	5	T. Ofenböck; "Terminal Sterilisation of Parenteral Drugs"; Process Tech. Online; February 18, 2022; https://process-technology-online.com/pharma/terminal-sterilisation-of-parenteral-drugs/; (5 pages).	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/SVETLANA M IVANOVA/	Date Considered	12/13/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Par Health Inc. Ex. 1002-0253

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2024-11-22
Name/Print	Sheena X. Wang	Registration Number	82,893

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Par Health Inc. Ex. 1002-0254

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Web Search History

date, time	web site	search string
12/13/2024 1:36:03 PM	Google	why was ketalar not developed as a ready-to-use product
12/13/2024 8:20:42 PM	Google	polypropylene styrene
12/13/2024 9:37:03 PM	Google	ketamine ready to use

Par Health Inc. Ex. 1002-0256

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 12/19/2024

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/19/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0257

Office Action Summary	Application No. 18/770,514	Applicant(s) DUSCI, Sergio	
	Examiner SVETLANA M IVANOVA	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/25/2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20,23-29 and 31-32 is/are pending in the application.

5a) Of the above claim(s) 26-28 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Par Health Inc. Ex. 1002-0258

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Response to Arguments

Applicant has amended the claims, and made arguments against the claims as amended. In view of Applicant's claim amendments modified rejections have been made below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8, 18-20, 23-25, 29 and 31-32 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record), or in the alternative under 35 U.S.C. 103 as being unpatentable over

Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record).

Ketalar is an FDA label for ketamine hydrochloride injection. Ketalar discloses preparing a Ketalar product/ (vial or for infusion) for induction of anesthesia by diluting Ketalar with sterile water for injection, USP, normal saline, USP, and dextrose in water. For maintenance of anesthesia, it discloses: "To prepare a dilute solution containing 1 mg of ketamine per mL, aseptically transfer 10 mL from a 50 mg per mL vial or 5 mL from a 100 mg per mL vial to 500 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (Normal Saline) and mix well. The resultant solution will contain 1 mg of ketamine per mL Use immediately after dilution. When fluid restriction is required, KETALAR can be added to a 250 mL infusion as described above to provide a KETALAR concentration of 2 mg/mL." (p. 3). Ketalar is diluted in sterile water. (*Id.*). Ketalar states that ketamine hydrochloride is formulated as slightly acidic (pH 3.5-5.5).

Further regarding infusion, Ketalar discloses that Ketalar should be given by slow microdrip infusion technique at a dose of 0.1 to 0.5 mg/ minute to maintain general anesthesia. (p. 3). To one of skill in the art, this description, and the above description of addition to the ketamine product a 250 mL infusion, indicates by the use of an infusion container/ bag.

Since Ketalar discloses a product with the same ingredients, it will also have the same osmolality, as per Applicant's claim 8, the same shelf life, as per Applicant's claims 21 and 22, the same chemical stability, as per Applicant's claim 23, the same average number of particles following storage of the ketamine product, as per

Applicant's claim 24, the same ketamine content after accelerated storage, as per Applicant's claim 25, and the same shelf-life, as per Applicant's claim 30.

Applicant's claim 1 recites that the ketamine product is ready-to-use (RTU). It is noted that the broadest reasonable interpretation of this claim term does include a RTU product as prepared in the description above, i.e. one which is pre-mixed and prepared for immediate use after dilution. This BRI renders Applicant's claims anticipated. However, Applicant's RTU limitation was not previously interpreted as anticipated, even before the instant claim amendments as the Examiner took into consideration the possibility that RTU be interpreted as pre-mixed, pre-diluted. Specifically, the office action previously provided.

Even if RTU is interpreted to mean pre-mixed, pre-diluted, it would have been obvious to a person of skill in the art before the effective filing date of the claimed invention, based on the disclosure of Ketalar, to prepare such a product with a reasonable expectation of success. Ketaler essentially teaches this product made just prior administration, based on which it would have been obvious to the skilled artisan to also prepare the pre-diluted product as well guided by considerations of ease of administration. Ketalar further renders obvious Applicant's claim 18, 19 and 29- that the ketamine product is autoclaved, and that the infusion container/ bag is terminally sterilized, or that the ketamine product is aseptically filled, since it teaches that the Ketaler product is USP grade and sterile, sterility of a product is a known function of autoclaving to one of skill in the art, and FDA approved injections/ infusions for *in vivo* administration in humans are for sterile/ aseptic products.

Applicant has presently amended the claims to recite wherein limitations of half-life storage stability of the RTU product. It is noted, however, that the claimed wherein limitations of half-life storage stability of the RTU product are merely functional limitations of a ketamine product with the recited features. The office action already presented a strong *prima facie* case to prepare a ketamine product, as recited. To the extent that the only difference of the Ketalar product of the prior art, and the instant claims is just the RTU feature, it is further significant that the prior art of record does require that this product be diluted prior to administration to the amounts. That Applicant presents features that the diluted product has a storage stability of [x] under conditions of [y], are merely just functional limitations of the does not take away from this strong *prima facie* case of obviousness. Applicant's reasons to combine, and the Examiner's reasons to combine, need not be the same. This motivation need not be express and may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000). See also In re Beattie,* 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor."). In the instant case, the office action already provided a rationale that it would have been obvious to the skilled artisan to also prepare the pre-diluted product as well guided by considerations of ease of administration. For Applicant to be able to rebut this *prima facie* case of obviousness Applicant would need to be able to show unexpected results of stability/ shelf-life under the same storage

conditions as compared to the closest art of record, namely, the Ketalar product. Neither Applicant's specification, nor Applicant's attorney arguments, provide any such data.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7 and 9-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar", of record), as applied to claims 1-6, 8, 18-20, 23-25, 29 and 31-32 in the 35 U.S.C. 103 rejection above, and further in view of US 11,207,309 B2 to Conrad et al. ("Conrad", of record).

Ketalar is discussed in the 35 U.S.C. 103 rejection above.

Ketalar discloses administration by infusion, but does not specifically disclose the characteristics of the infusion container/ bag of Applicant's claims 7 and 9-17.

For starters, it is noted that what is disclosed as subject matter in these claims, even per Applicant's own specification is in fact commercially available infusion bags.

[00047] In one aspect, the intravenous bag is made up of multilayer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer.

Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

> infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation; an M315 film manufactured by SealedAir Corporation; an APP-series film manufactured by Polycine, such as APP-114S film manufactured by Polycine; a polypropylene film, such as those manufactured by Technoflex, such as an Inerta® film manufactured by Technoflex; a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa; an Inerta 103 film, made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer, which may be manufactured by Technoflex; or another commercially-available polymer film designed for use in intravenous bag products. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the infusion bag.
>
> **[00054]** In certain aspects, the infusion container (e.g., infusion bag) is contained in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

Conrad relates to parenteral liquid formulations of fentanyl, which are stable formulations supplied as a ready-to-administer product in an infusion container or bag. The stable formulations are terminally sterilized in the infusion container. (Abstract). Conrad further discloses wherein the formulation is stored in an infusion container and

terminally sterilized, for example, by autoclaving. Conrad specifically discloses an infusion bag, per Applicant's claims.

TABLE 7

Component	Description
IV bag and tube	100 cc: Polycine APP114 multilayer polyolefin/ styrene block copolymer, 200 µm Tube: APP107, 1000 µm 250 cc: Polycine APP114 multilayer polyolefin/ styrene block copolymer, 200 µm Tube: APP107, 1000 µm
Twist-off stopper	Polypropylene twist-off, TP823
Overwrap	Film 140 MM Width × 265 MM, Climaprop II (12PET/9ALU/80PE) Film 140 MM Width × 290 MM, Climaprop II (12PET/9ALU/80PE)

Conrad further discloses a twist-off closure with the characteristics of Applicant's claim 11. "The formulations of the present invention can be filled in an infusion containing a head space. Storing injectable solutions in containers generally requires an inert head space (e.g., nitrogen or argon) to reduce the loss of stability. The fentanyl formulations can be filled into infusion containers by conventional methods without the need for filling under inert gas and purging of the head space to eliminate the presence of oxygen, for example, below 5 percent. As such, the fentanyl formulations can be utilized with a broad range of filling procedures without the need for modifying equipment or operating procedures to accommodate for inert gas filing conditions." (col. 11, ll. 14-26). "Containers are sealed as typical in the industry, for example, with the use of a lid, cap, closure and the like. Polymeric bags such as those manufactured by Technoflex and Polycine." (col. 8, l. 67-col. 9, l. 3).

Per Conrad, the polymeric infusion bag can have an aluminum overpouch. Per Conrad, example materials for the containers and container components can include polyolefins, polysulfone, polycarbonate, polypropylene, polyethylene (LDPE or HDPE), ethylene/propylene copolymers, acrylic-imide copolymers, polyester (e.g. PET, PEN and the like), Teflon, Nylon, acetal (Delrin), polymethylpentene, PVDC, ethylvinylacetate, AN-copolymer or polyoprene. Preferably, the materials for the container and container components are suitable to withstand aseptic filling and not deform during terminal sterilization. (col. 6, ll. 40-56).

Even though Conrad does not specifically disclose that the infusion bag is 3-layers, and that the overwrap 4-layers, or that at least one layer comprises polyropylene styrene-block copolymer, as can be seen from the above disclosure, Conrad specifically discloses that the infusion bag is multilayer, that the overwrap is at least two layers and that an additional layer is one of aluminum, as well as names other possible layers with polyester, polypropylene, etc. (col. 6, ll. 40-56)., as well as styrene block copolymer (Table 7).

Accordingly, it would have been obvious to a person of skill in the art before the effective filing date of the claimed invention to modify the teachings of Ketalar and Conrad in order to practice Applicant's claimed invention with a reasonable expectation of success. The skilled artisan would have been motivated to do so, because Ketalar teaches preparing a RTU ketamine product as an infusion, and Conrad discloses that infusion bags/ containers of different kinds, to include the specific one claimed in Applicant's claims, are readily commercially available in the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SVETLANA M IVANOVA whose telephone number is (571)270-3277. The examiner can normally be reached 8:30-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SVETLANA M IVANOVA/
Primary Examiner, Art Unit 1627

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2

CONFIRMATION NO. 2594

6449
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

PUBLICATION NOTICE



Date Mailed: 01/23/2025

Title:READY-TO-USE KETAMINE PREMIX FORMULATION

Publication No.US-2025-0025431-A1
Publication Date:01/23/2025

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently https://patentcenter.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

Further assistance in electronically accessing the publication, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Par Health Inc. Ex. 1002-0270

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	18/770,514
	Filing Date	July 11, 2024
	First Named Inventor	Sergio DUSCI
	Art Unit	1627
	Examiner Name	SVETLANA M IVANOVA
	Practitioner Docket No.	4830-114US2

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 82,893.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Sheena X. Wang/ — Signature

February 10, 2025 — Date

Sheena X. Wang — Typed or printed name

202-783-6040 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**02/10/2025 03:44:58 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Giovanelly Castell
PATENT CENTER #	69120642	FILING DATE	07/11/2024
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Sheena Wang

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-114US2-Ecomm_Auth_From.pdf	2	Internet Communications Authorization	825 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
4830-114US2-Ecomm_Auth_From.pdf	C1AA0BDA5812E449EB6607D4697492DD53AFBC19E2848ED961B73411856D9757B3FB7993428026ADF277B3868ED6A5E4EB7467E04CAF6B436DFAFDB7B1728705

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 02/14/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
02/14/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0275

Applicant-Initiated Interview Summary	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio		
	Examiner SVETLANA M IVANOVA	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
SVETLANA M IVANOVA	Primary Examiner	Telephonic
SHEENA WANG	Attorney of Record	
AYDIN HARSTON	Attorney of Record	

Date of Interview: 11 February 2025

Issues Discussed:

Other

Applicant called to discuss proposed claim amendments and a path to allowance. Prior to the interview, Applicant submitted its arguments by email. The arguments were made by Sheena Wang. The submissions are attached hereto.

The Examiner noted that the proposed claim amendments, geared towards a preservative-free formulation, will required further consideration and search. She noted that the a preliminary google search indicates that preservative-free ketamine formulations are available in the art. As a non-limiting example Applicant noted https://academic.oup.com/bja/article/92/1/152/252063, which provides for one such composition, and notes as to the common preservative benzethonium chloride that it was associated with toxicity. Applicant noted that this formulation appeared to have been used for intrathecal injection, and that this by itself could have been the factor associated with toxicity because the injection was to the brain. While the Examiner did not make this point during the interview, she brings it to Applicant's attention now in preparing a summary of the record, as there is a point on this reference, which appears to point to far wider use. "We have used preservative-free caudal ketamine for over 330 general surgical, urological and orthopaedic paediatric cases in Chelmsford since 1998, providing excellent, prolonged analgesia with no untoward effects."

Applicant stressed that further to the interview summary, there are two aspects to consider as to the instant formulation: 1) that it is preservative-free, and 2) that it is ready to use, and with no need for dilution. She asked that both be considered in assessment of the art. The Examiner agreed that the totality of the arguments will be considered. The Examiner also noted that a number of other references on a preliminary google search seem to point to preservative-free ketamine formulations, and asked that Applicant too do its due diligence on this issue before filing a response.

The Examiner also made a notation as to Applicant's specification. To take as an example paragraph [0011] it provides that "In one aspect, the ketamine product of the disclosure is free of a preservative or antimicrobial such as benzethonium chloride." The Examiner asked that the language leaves some ambiguity whether benzethonium chloride is considered both a a preservative and an antimicrobial, and asked that Applicant's response specifically note that the Examiner confirms that the term "preservative" encompasses within its meaning "antimicrobial", to include benzethonium chloride specifically.

Par Health Inc. Ex. 1002-0276

Applicant-Initiated Interview Summary	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio		
	Examiner SVETLANA M IVANOVA	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** **2 of 2**

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Par Health Inc. Ex. 1002-0277

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	18/770,514	Filing Date	2024-07-11	Docket Number (if applicable)	4830-114US2	Art Unit	1627
First Named Inventor	Sergio DUSCI			Examiner Name	SVETLANA M IVANOVA		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☒ Other CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e)

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 022135

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Par Health Inc. Ex. 1002-0278

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2025-03-14
Name	Sheena X. Wang	Registration Number	82,893

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Par Health Inc. Ex. 1002-0280

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	: 18/770,514
1ST NAMED INVENTOR	: Sergio DUSCI
FILED	: July 11, 2024
ART UNIT	: 1627
EXAMINER	: SVETLANA M IVANOVA
CONFIRMATION NO.	: 2594
DOCKET NO.	: 4830-114US2
CUSTOMER NO.	: 6449

AMENDMENT WITH A REQUEST FOR CONTINUED EXAMINATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated December 19, 2024, please enter the following amendments and remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.
2. (Original) The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.
3. (Original) The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. (Currently Amended) The ketamine product of claim 1, wherein the aqueous ketamine solution is ~~preservative-free or~~ antimicrobial-free.
5. (Cancelled)
6. (Original) The ketamine product of claim 1, wherein the pH of the aqueous ketamine solution is about 3 to about 6.
7. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
8. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
9. (Original) The ketamine product of claim 7, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
10. (Original) The ketamine product of claim 7, wherein the closure comprises a plastic material.

Par Health Inc. Ex. 1002-0282

11. (Original) The ketamine product of claim 7, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

12. (Original) The ketamine product of claim 10, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

13. (Previously Presented) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

14. (Original) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

15. (Previously Presented) The ketamine product of claim 7, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises polypropylene styrene-block copolymer.

16. (Original) The ketamine product of claim 7, wherein the infusion bag is contained within an overwrap.

17. (Original) The ketamine product of claim 16, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

18. (Original) The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

19. (Previously Presented) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

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20. (Original) The ketamine product of claim 19, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

21. (Cancelled)

22. (Cancelled)

23. (Original) The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

24. (Original) The ketamine product of claim 1, wherein the average number of particles equal to or greater than 10 µm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months; and/or

the average number of particles equal to or greater than 25 µm does not exceed 600 per container following storage of the ketamine product at room temperature for 24 months.

25. (Previously Presented) The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater compared to the ketamine content before storage.

26. (Withdrawn) A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

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27. (Withdrawn) The method of claim 26, wherein the step of terminally sterilizing comprises autoclaving the infusion bag at a temperature between about 110 to about 130° C for a period of time of about 7 to about 60 minutes.

28. (Withdrawn) A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

29. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

30. (Cancelled)

31. (Previously Presented) The ketamine product of claim 19, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

32. (Previously Presented) The ketamine product of claim 29, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

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REMARKS

Claims 1-4, 6-20, 23-29, and 31-32 are pending. Claims 1, 4 and 29 have been amended. Claims 5, 21, 22 and 30 are cancelled. Claims 26-28 are withdrawn from consideration. Support for all amendments is found throughout the specification as filed and original claims 4, 19 and 30; and paragraphs [0009], [0014], [0044], [0045], [0057], [0058], [0059], [0112]-[114], Examples 1-5 and figures 1-4 and 7 of the specification. A total of 28 claims are pending. No new matter has been added.

The Applicant has not publicly dedicated or abandoned any unclaimed subject matter or acquiesced to any objection or rejection set forth in the Office Action. The Applicant expressly reserves the right to pursue prosecution of any presently or previously unelected, excluded, or cancelled claim embodiments, and/or species, in one or more future continuation and/or divisional applications.

In response to the Office Action, favorable reconsideration and allowance of the present application are respectfully requested.

For the reasons discussed below, it is submitted that this application is in condition for allowance.

Interview Summary

Applicant and Applicant's representative wish to thank Examiner Ivanova for the courtesies extended during the telephonic interview held on February 11, 2025. During the interview, Applicant's representative and the Examiner discussed the Office Action, the rejections under 35 U.S.C. § 102(a)(1) or in the alternative under 35 U.S.C. § 103 over Ketalar, and the rejection under 35 U.S.C. § 103 over Ketalar further in view of Conrad, and the proposed amendments to claims 1 and 29. The Examiner agreed that Ketalar, after dilution, does not have

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a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C and also that it comprises benzethonium chloride, which is known in the art to be a preservative and antimicrobial.

The Examiner also agreed that the proposed amendment to claims 1 and 29 to recite that the ketamine solution is preservative-free would overcome the anticipation rejection over Ketalar.

Regarding the obviousness rejections, the Examiner asserted that additional references may be found regarding preservative-free ketamine formulations. In response, Applicant's representative emphasized that the preservative free-ketamine product of the pending claims is a sterile and ready-to-use (RTU) product, comprises about 0.5 to about 2.5 mg/mL of ketamine, and has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C. The Examiner conducted a preliminary google search during the interview and mentioned several references. *See, e.g.*, Huddy, *et.al*, *Preservative-free ketamine*, 92 BRITISH J OF ANAESTHESIA 1, 152 (2004) (hereinafter "Huddy") and Malinovsky, et al., *Is ketamine or its preservative responsible for neurotoxicity in the rabbit?*, 78 ANESTHESIOLOGY 1, 109-115 (1993). The Applicant's representative and the Examiner briefly discussed the references that the Examiner found during the call, focusing on Huddy.

The Examiner asked the Applicant to conduct further due diligence regarding preservative-free ketamine formulations.

The Examiner stated that it was her impression that further search and consideration would be required to determine whether the amendment to claims 1 and 29 and the arguments discussed during the interview and detailed below would overcome the obviousness rejection over Ketalar. The Examiner agreed to focus the search on preservative-free, ready-to-use,

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ketamine products comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature.

Applicant now files this Response with a Request for Continued Examination to further address the Examiner's comments.

Response to Claim Rejections – 35 U.S.C. § 102(a)(1) Based on NDA016812 ("Ketalar")

Claims 1-6, 8, 18-20, 23-25, 29 and 31-32 were rejected under 35 U.S.C. § 102(a)(1) as allegedly being anticipated by Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar"). Ketalar discloses preparing a ketamine product (vial or for infusion) for induction of anesthesia by diluting Ketalar with sterile water for injection, USP, normal saline, USP, or dextrose in water.

Applicant traverses this rejection because the cited art, considered alone or in combination, does not teach and would not have suggested all of the features of independent claims 1, 19 and 29 as currently amended. "To reject a claim as anticipated by a reference, the disclosure must teach every element required by the claim under its broadest reasonable interpretation." MPEP § 2131. Furthermore, the MPEP also requires the "consideration" of every claim feature in an obviousness determination. MPEP § 2143.03. To render independent claims 1, 19 and 29 unpatentable, Ketalar must **teach or suggest each and every claim feature**. *See In re Royka*, 490 F.2d 981 (CCPA 1974). Here, the diluted ketamine solution described in Ketalar does not teach or suggest at least the "preservative-free" and "wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C" limitations required by claims 1 and 29, as amended, and claim 19.

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On pages 3-4 of the Office Action, the Office asserts that "[s]ince Ketalar discloses a product with the same ingredients, it will also have the same osmolality, as per Applicant's claim 8, the same shelf life, as per Applicant's claims [1, and original cancelled claims] 21 and 22, the same chemical stability, as per Applicant's claim 23, the same average number of particles following storage of the ketamine product, as per Applicant's claim 24, the same ketamine content after accelerated storage, as per Applicant's claim 25, and the same shelf-life, as per Applicant's claim 30." Applicant respectfully disagrees as discussed further below. Additionally, independent claims 1, 19 and 29, as amended, state that "the ketamine solution is preservative-free." In contrast, Ketalar contains "not more than 0.10 mg/mL benzethonium chloride **added as a preservative** in water for injection." Ketalar at p. 10 (emphasis added). Thus, at least because Ketalar contains a preservative and the claims, as amended, require a solution that is preservative-free, the anticipation rejection has been rendered moot. Applicant respectfully requests withdrawal of the rejection.

Response to Claim Rejections – 35 U.S.C. § 103 Based on NDA016812 ("Ketalar")

Claims 1-6, 8, 18-20, 23-25, 29 and 31-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Ketalar. The Office Action acknowledges that **Ketalar requires dilution prior to use**. O.A. at p. 3. Furthermore, the Office Action acknowledges that the **Ketalar product needs to be used immediately after dilution**. *Id.* at 4.

On page 4, the Office Action explains various different interpretations of the claim limitation of "ready-to-use." It appears that the Office has overlooked that the specification sets forth an express definition as follows:

> As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which

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the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

MPEP 2111.01(IV)(A) states that "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim." Thus, the Office Action's various different interpretations are unnecessary and irrelevant where the only definition that controls is the one that is expressly provided in the specification. *Id.*

Applicant traverses the rejection because Ketalar does not teach and would not have suggested all of the features of claims 1, 19 and 29, from which claims 2-6, 8, 18, 20, 23-25 and 31-32 depend.

First, Ketalar only teaches a concentrated ketamine product that must be diluted prior to use and used immediately after dilution. Ketalar does not disclose and would not have suggested the claimed product that is a ready-to-use product comprising a ketamine solution having about 0.5 to about 2.5 mg/mL of ketamine, wherein the ketamine solution is preservative-free, and wherein the ketamine product has a shelf-life of more than six months under the specified conditions. Applicant submits that a person of ordinary skill in the art would understand that a preservative-free formulation would have different shelf-life, chemical stability, average number of particles following storage, and/or ketamine content after accelerated storage characteristics compared to a formulation with preservatives, such as Ketalar. Furthermore, a person of ordinary skill in the art would not expect a preservative-free formulation to have increased shelf-life compared to a formulation containing a preservative such as Ketalar.

Additionally, a person of ordinary skill would recognize that Ketalar is not, and does not suggest, a ketamine product comprising an aqueous ketamine solution **comprising about 0.5**

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to about 2.5 mg/mL ketamine, wherein the ketamine product **is sterile** and **ready-to-use (RTU)**, and **has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C**. Ketalar describes a concentrated ketamine solution that would not inherently have the same shelf-life as the ketamine product of claims 1-6, 8, 18-20, 23-25, 29 and 31-32 **after dilution**. Indeed, as discussed below, the claimed shelf life also would not have been obvious for the sterile, low-concentration ready-to-use solutions claimed. The Ketalar label specifies that a physician should "not administer the 100 mg/mL concentration of KETALAR intravenously without proper dilution… [and m]ust be **used immediately after dilution.**" Ketalar at p. 2 (emphasis added). Therefore, Ketalar does not teach a ready-to-use[1] product comprising a ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine that also has "a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C" of amended independent claims 1 and 29 and independent claim 19 because it has to be used immediately.

Second, a person skilled in the art of injectable formulation development would not look to Ketalar, a concentrated product that requires admixing or compounding before use, to arrive at the low concentration and ready-to-use (RTU) solutions having the shelf-life or stability characteristics of the instant invention. There is lack of scientific comparability between admixed or compounded drugs, on the one hand, and sterile, ready-to-use injection products on the other hand. *First*, Ketalar only teaches to dilute the formulation immediately prior to use. It does not teach that the product should be prepared at a registered compounding pharmacy or

[1] Again, the specification defines the term as follows: As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

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that it should be sterilized following dilution. *Second*, Ketalar contains a preservative. *Third*, as explained by the FDA, even if drug products are compounded at a registered outsourcing facility and terminally sterilized (which Ketalar does not teach or suggest), the expiration date of compounded drug products that do not contain preservatives, but are terminally sterilized by the compounding facility, should be **at most 14 days** after release at room temperature when sterility testing is not completed, and **not more than 28 days** beyond the completion of a sterility test when one is completed. *See* DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA-2022-D-0219, TEMPORARY POLICIES FOR COMPOUNDING CERTAIN PARENTERAL DRUG PRODUCTS; GUIDANCE FOR INDUSTRY, at 12 (2024) (hereinafter "FDA Policies 2024"); *see also* DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA-2014-D-0779, CURRENT GOOD MANUFACTURING PRACTICE—GUIDANCE FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT, at 44 (2020) (hereinafter "FDA Interim Guidance"). As illustrated by the FDA Interim Guidance (which was in effect at the priority date), drug compounding manufacturers do not necessarily terminally sterilize or complete stability or sterility testing on their products before the product is released. *See* FDA Interim Guidance at 44 (identifying acceptable beyond use dates (BUD) under various circumstances).

Furthermore, Ketalar does not instruct the user to sterilize the diluted solution or complete stability or sterility testing before use. Terminal sterilization techniques, such as autoclaving, subject the product to rigorous conditions (e.g., high temperature) that may degrade the product, and may have different and unpredictable effects depending on the particular active ingredient, the excipients, the container system, and the combination thereof. The cited art does not provide any information regarding terminal sterilization of a ketamine product, and in

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particular does not provide information regarding terminal sterilization or autoclaving of a ketamine product containing 0.5 to 2.5 mg/mL ketamine as required by claims 2 and 18-20.

Furthermore, as explained by the United States Pharmacopeia, Chapter ⟨797⟩ Pharmaceutical Compounding—Sterile Preparations (USP Revision Bulletin, 2008) ("USP"):

> When attempting to predict a theoretical BUD [beyond-use date], a compounded or ***admixed preparation should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components***. For example, antioxidant, buffering, or antimicrobial properties of a sterile vial for injection (SVI) might be lost upon its dilution, with the potential of seriously compromising the chemical stability of the SVI's active ingredient or the physical or microbiological stability of the SVI formulation in general. ***Thus, the properties stabilized in the SVI formulation usually cannot be expected to be carried over to the compounded or admixed preparation***.

See USP at 41 (emphasis added).

Therefore, admixed and compounded products are well known to lack the same stability as the sterile and ready-to-use (RTU) products recited in amended independent claims 1 and 29 and independent claim 19. There is no evidence that the Ketalar product referenced in the Office Action, after dilution to the ketamine concentration of the recited claims, would meet either the sterility or the stability requirements identified in the recited claims. And if one were to dilute it, then it would not meet the definition of "ready-to-use" as required by the claims where the applicant has acted as its own lexicographer to provide the controlling definition: As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the

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product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration). *See* MPEP 2111.01(IV)(A).

Ketalar does not provide a person of ordinary skill with any guidance, suggestion, or motivation to prepare the claimed **sterile, ready-to-use, preservative-free** ketamine composition **comprising about 0.5 to about 2.5 mg/mL ketamine** that **can be stored for at least six months when stored at a controlled room temperature between 15–30°C**. In fact, Ketalar repeatedly notes that the diluted ketamine solution must immediately be administered to the subject and is **not** suitable for prolonged storage. And the Office's reliance on a dilution step means that the proposed modification to the prior art results in something that does not meet the definition of ready-to-use required by the claims.

Third, Applicant also submits that the claimed ready-to-use premix composition provides for surprising and unexpected advantages over the concentrated compositions in the cited art. For example, the claimed preservative-free RTU ketamine composition provides advantages in the ability to be stored over prolonged periods of time while maintaining stability at low, ready-to-use concentrations of ketamine. For example, Example 3 of the instant application studied the long term and accelerated stability of diluted, commercially-available, preservative-containing ketamine solutions compared to the preservative-free ketamine product of the instant application and concluded that "Tables 6-9 surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride under accelerated conditions and long-term storage." *See* Application No. 18/77,514 at [0114]. Such advantages over the concentrated multiple-dose vial compositions of the prior art are

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further evidence of the non-obviousness of the claims over the cited references. *See* M.P.E.P. § 716.02(a).

Thus, the prior art does not teach all of the elements of the claimed invention. Indeed, the prior art specifically teaches away from storing a diluted ketamine solution at room temperature for prolonged periods (e.g., at least six months as required by all pending claims, or twenty-four months as recited in dependent claims 23, 31, and 32). Furthermore, Applicant respectfully submits that the disclosures in Ketalar fail to provide reasonable guidance that would have motivated a skilled artisan to modify Ketalar, as alleged, with a reasonable expectation of success to achieve the claimed invention. Thus, the claimed invention is not rendered obvious by the teachings of Ketalar.

All remaining claims under consideration (claims 2-20, 23-25, and 31-32) are dependent from one of claims 1, 19, or 29, and are therefore nonobvious for at least the same reasons. Therefore, Applicant respectfully requests that the rejections be withdrawn for at least these reasons.

Response to Prior Art Discussed During Examiner Interview– Concentrated preservative-free ketamine does not render obvious the pending claims

In response to the internet search for mentions of preservative-free ketamine compositions that the Examiner conducted during the telephonic interview held on February 11, 2025, Applicant first notes that there is only one FDA approved injectable pharmaceutical drug product containing ketamine hydrochloride (New Drug Application (NDA) number 016812), which is packaged in 10 mg/ml, 50 mg/ml or 100 mg/ml multi-dose vials, which requires dilution before use, must be used immediately following dilution, and contains the preservative benzethonium chloride. *See* Ketalar (ketamine hydrochloride) injection, for intravenous or

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intramuscular use, CIII, NDA016812, at 1,2 and 10, (2022). The Ketalar formulation is different for multiple reasons explained above from the claimed preservative-free, sterile and ready-to-use (RTU) ketamine product. Additionally, there is currently no FDA-approved sterile and ready-to-use (RTU) ketamine solution, either with or without a preservative.

In response to the Examiner's request to conduct further due diligence on preservative-free ketamine compositions, Applicant has identified certain scientific journal articles discussing preservative-free ketamine, none of which describes a ketamine product that meets the limitations of the pending claims. *See, e.g.*, Errando, et al., *Some misleadings about ketamine and their preservatives/Response*, 23 *Regional Anesthesia and Pain Medicine* 3, 323 (1998) (hereinafter "Errando"); and Gomes, *et al.*, *Neurotoxicity of subarachnoid preservative-free S (+)-ketamine in dogs*, 14 PAIN PHYSICIAN 1, 83 (2011) (hereinafter "Gomes"). The preservative-free ketamine used in Gomes was **packaged in a 50 mg/ml ampoule** and diluted in saline prior to intrathecal application. *See* Gomes at 84-85. Huddy and Errando were letters to the editor and did not describe the method of their referenced studies in detail. The studies that Huddy and Errando referenced include (1) De Beer, et al., *Caudal additives in children—solutions or problems*?, 90 BRITISH J. OF ANAESTHESIA 4, 487-498 (2003); (2) Stotz, et al., *Histological findings after long-term infusion of intrathecal ketamine for chronic pain: a case report*, 18 J. OF PAIN AND SYMPTOM MANAGEMENT 3, 223-228 (1999); and (3) Malinovsky, et al., *Is ketamine or its preservative responsible for neurotoxicity in the rabbit?*, 78 ANESTHESIOLOGY 1, 109-115 (1993). The preservative-free ketamine used in each of these studies was **packaged in a concentrated form** then diluted with saline or distilled water prior to use. Nothing in the references indicates that the diluted preservative-free ketamine was stored for any length of time prior to use or that it was sterile following dilution. *Id.* Thus, none of these publications relates to

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a sterile and ready-to-use (RTU) ketamine product comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature.

As explained above with respect to Ketalar, the concentrated preservative-free ketamine formulations referenced in the prior art do not teach, suggest, or render obvious a sterile, RTU preservative-free ketamine formulation, comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature. A person of ordinary skill in the art would not expect a diluted formulation to have the same stability characteristics of a concentrated formulation, even if it contains the same components. *See* USP at 41; FDA Policies 2024 at 12.

In response to the Examiner's request to clarify the role of benzethonium chloride in a ketamine product, such as Ketalar, Applicant submits that it is known in the art that benzethonium chloride is a preservative and an antimicrobial that has "broad-spectrum antimicrobial properties against bacteria, fungi, and viruses." Merchel Piovesan Pereira, *et. al.*, *Benzalkonium chlorides: uses, regulatory status, and microbial resistance*, 85 APPLIED AND ENVIRONMENTAL MICROBIOLOGY 13, at 1 (2019). As noted above, Ketalar refers to benzethonium chloride as a preservative.

Response to Claim Rejections – 35 U.S.C. § 103 Based on Ketalar and Conrad

Claims 7 and 9-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ketalar further in view of US 11,207,309 B2 to Conrad *et al.* ("Conrad"). The Office notes that Ketalar is discussed in the above section and acknowledges that it does not disclose the characteristics of the infusion bag of claims 7 and 9-17. O.A. at p. 6. The Office further acknowledges that Conrad relates to parenteral liquid formulations of **fentanyl**. O.A. at p. 8. However, the Office notes that this fentanyl product is supplied as a terminally sterilized ready-to-administer product in an

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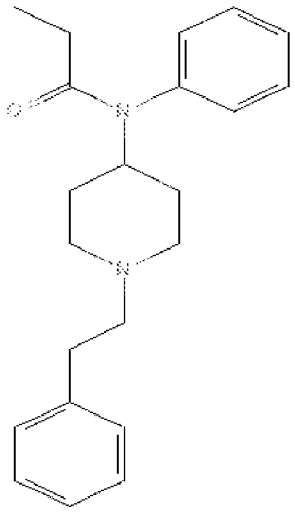
infusion container that has the characteristics of claims 7 and 9-17, including the twist-off closure and aluminum overpouch. *Id.* at 9-10.

First, amended independent claim 1 is not anticipated or rendered obvious by Ketalar. Conrad is only cited as allegedly disclosing stable fentanyl formulations supplied as a ready-to-administer product in an infusion container or bag and is not alleged to and does not remedy the deficiencies of Ketalar. Claims 7 and 9-17 depend directly or indirectly on independent claim 1. Thus, Applicant respectfully requests withdrawal of the rejection of claims 7 and 9-17.

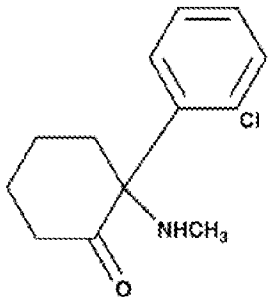
Second, Conrad relates to stable **fentanyl** formulations and does not remedy the deficiencies of Ketalar because Ketalar is directed to a different active ingredient, **ketamine**. The Office ignores the art-recognized difficulties in creating stable ready to use formulations of specific drugs, accounting for each drug's chemical properties, specific excipients in the formulation, and selection of drug containers. "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353, 1359 (Fed. Cir. 2008) (quoting *KSR,* 550 U.S. at 420).

Fentanyl is chemically known as N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propenamide and has the chemical structure shown below:

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In contrast, ketamine is known as (±)-2-(*o*-Chlorophenyl)-2-(methylamino)cyclohexanone and has the chemical structure shown below:



A person of ordinary skill in the art would understand that fentanyl and ketamine would be expected to have different degradation pathways and to react chemically differently with excipients and infusion containers. A person of ordinary skill in the art would understand that a formulator must consider physical stability, chemical stability, and microbiological stability in light of all of the components in a formulation, including the potential leachables and extractables associated with the packaging materials. Drug products comprising ketamine and fentanyl are complex systems that include numerous chemical species co-existing in a range of interdependent equilibrium processes, which may be affected by the interaction of the drug components and with potential leachables and extractables associated with the packaging

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materials. In addition to the chemical differences of the active ingredient, the excipients included in the formulation of independent claim 1 and Conrad are different. For example, the Conrad formulation comprises about 0.5 mg/mL to about 5 mg/mL of a buffer. *See* Conrad at claim 1. In contrast to Conrad, the invention of independent claim 1 does not require buffer excipients. A person of ordinary skill in the art would understand that the presence of a buffer may affect the stability characteristics and packaging materials considerations for a ready to use (RTU) drug product. For at least this additional reason, Applicant respectfully requests withdrawal of the rejection of claims 7 and 9-17.

Accordingly, Applicant respectfully submits that the rejections of record should be withdrawn for at least the foregoing reasons.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections, and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

If any fees are required, such as, but not limited to, any extension of time fee under 37 C.F.R. 1.17, Applicant hereby petitions for an extension of time, if necessary, and authorizes the Office to charge all required fees to deposit account number 02-2135.

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Respectfully submitted,

By: /Sheena X. Wang/

Sheena X. Wang
Attorney for Applicant
Registration No. 82,893
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.,
Suite 900 East
Washington, D.C. 20001
Telephone: (202) 783-6040
Facsimile: (202) 783-6031

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/770,514	Filing Date 07/11/2024	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	03/14/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 30	= 0		x $200 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $600 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CAROLYN E THOMAS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**03/14/2025 04:10:12 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	69584978	FILING DATE	07/11/2024
CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Sheena Wang

Documents

TOTAL DOCUMENTS: 15

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2025-03-12 Ketamine R to Final OA_CLEAN.pdf	21	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	142 KB
4830-114US2 RCE Transmittal.pdf	3	Request for Continued Examination (RCE)	1628 KB
4830-114US2 Track One Request.pdf	2	Track One Request	194 KB
4830-0114US2 IDS transmittal.pdf	1	Transmittal Letter	16 KB
4830-0114US2 IDS.pdf	6	Information Disclosure Statement (IDS) Form (SB08)	1274 KB

1 Errando-NPL.pdf	1	Non Patent Literature	268 KB
2 Gomes-NPL.pdf	8	Non Patent Literature	531 KB
3 Pereira-NPL.pdf	13	Non Patent Literature	978 KB
4 FDA-Compounding 2024-NPL.pdf	18	Non Patent Literature	268 KB
5 Malinovsky-NPL.pdf	7	Non Patent Literature	1195 KB
6 Huddy-NPL.pdf	1	Non Patent Literature	33 KB
7 Stotz-NPL.pdf	6	Non Patent Literature	2897 KB
8 De Beer-NPL.pdf	12	Non Patent Literature	134 KB
9 FDA 2020-NPL.pdf	51	Non Patent Literature	529 KB
10 USP 797-NPL.pdf	61	Non Patent Literature	921 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2025-03-12 Ketamine R to Final OA_CLEAN.pdf	8D7A1A27E6A396FA075F871241E8CC5185485321478755495EF330D2FB0C238810289B9C37B7CF14D6E3307A267B8EBF5E5C1A15D4ACB4A6C587D0088993E4FE
4830-114US2 RCE Transmittal.pdf	FBB81201F84AF283ADE06A44CB35FB3C012A6837A9D67987FBE71F7E7CC0AA163A7A915F614D0112389472A1F8AEAC5197E509E35DAC7BD5A1F224EC98D108B9
4830-114US2 Track One Request.pdf	6CAC82F89D6579CA1AECA9D22E3BA16879793660C3AAC0F2387DEC406451E245CD527B991F804DBBC5F21C5E60DB23B0F22C0C465FDD65FDF19C2C1F19B4C9DE
4830-0114US2 IDS transmittal.pdf	E43F8A73B9B9D523E0242559EA3D38BD0CE1F888C32B5EBA7231B3E77A5022786A024857FF7073FC5FA697CEC7CA16BE0B55D594A44291C440C4D6F8DCC3B647
4830-0114US2 IDS.pdf	707BCBF0D8677DDA1AA58C24343DC8882B6C9537A9F48BF95DB5692A8F8838B3C8BC1DFC85237329B69CAF74ABC236D20C7771184387F3390BC4391C6CEC19E6
1 Errando-NPL.pdf	FEDFFC21FC66CA4ED9F9866AD29DABCF0220A14A1CDEA7484964B3F19DEC07C7DFD2031767D8AFE9D7CD923D927D32316FCAFC8610067C6409B1AF826368EC45
2 Gomes-NPL.pdf	4CC06C43EEB6D853926D9B811C79CB3FC4E6B0DD0FE593414DFDAFC2202F51F8E2BFC365837C52E4518B8D57CC642ED1DF5E4518D258DC522FBADF4E42EB53DF

3 Pereira-NPL.pdf	0648966875047F11A8865C1671CD07684D92FD6D1CABA68AA BCD4CA77AF2E2EEECB5D3E5FDC1B35DE5945F9668DCF009 506BB0831467030622CDDA6BADB4EC22
4 FDA-Compounding 2024-NPL.pdf	0189A7516FB1B06D8669D80513A4A01036B7099BC849F8C799 E5176CB0CC7139B0FCCD95DB9AEA4AD3216EF2F408BD76E 83AC733446CB5F8DD6E025CCDB2474B
5 Malinovsky-NPL.pdf	76E3D8C6B8346A37E2ADD376DD9EA7BAF458024F7494EF6E D10440DEB2EB47E63D6D86DAC13E24C653C59600B18D0819 4BE5524FD1EDD4D500914F046BAC8F51
6 Huddy-NPL.pdf	DE32348CA22D0FC2C2F0777E913F54DA413E0176F2D21E285 027F63A219CC72B22B93C3A3D73670822B4AC439B2AE97657 31517894BA9F1B81F5ED0C0C2E1C33
7 Stotz-NPL.pdf	58ABC216FB689C38075BAC793DA5874EE229966D45743F27C 1F5A171FD5A19DEFB9E1F6EA4E9A29171CADE9CE75BA7A3F 191FA3EC883E418F397076A361AF8CA
8 De Beer-NPL.pdf	DE52274F43890D6D98FAE0D7A2AF3FE57B4795B4566D2DC7 BD4D3119FB67835413E3B06936B87A82F955303AD190F8BD0 E19D629CBA6FB8B0D3AEE99D7A8DC29
9 FDA 2020-NPL.pdf	76927B54C19F3BD21ABB4D751009885410FDA1681B9A796366 48C8E7B81A5E9D03B2CEB9723AF4590FB86A24C1CDA17F79 3AFD7777D673CA77FE7079B251D840
10 USP 797-NPL.pdf	A4761BA4F7CE576F18BFBA94108C2C199912083110BACC2F3 2DD5BA7C9457CE49DB11FBD3A975C7F93113E9FD783D213F 3A634893EFF85BEF96C364FC7A01887

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	18/770,514	Filing Date	2024-07-11	Docket Number (if applicable)	4830-114US2	Art Unit	1627
First Named Inventor	Sergio DUSCI			Examiner Name	SVETLANA M IVANOVA		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☒ Other CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e)

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 022135

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Par Health Inc. Ex. 1002-0306

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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Signature of Registered U.S. Patent Practitioner			
Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2025-03-14
Name	Sheena X. Wang	Registration Number	82,893

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Par Health Inc. Ex. 1002-0308

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 18/770,514
First-Named Inventor	: Sergio DUSCI
Filed	: July 11, 2024
TC/A.U.	: 1627
Examiner	: SVETLANA M IVANOVA
Docket No.	: 4830-114US2
Customer No.	: 6449
Confirmation No.	: 2594

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Under the provisions of 37 C.F.R. §§ 1.56, 1.97 and 1.98, Applicant submits herewith information that the Office may wish to consider in examination of the subject application. Materials submitted for consideration are listed on the attached form PTO-SB08.

Upon submission of the attached form PTO-SB08, the cumulative number of applicant-provided or patent owner-provided items of information under §1.98(a)(1) is 23.

Applicant certifies that no IDS size fee is required.

Respectfully submitted,

By: _____/Sheena X. Wang/_____

Sheena X. Wang
Attorney for Applicant
Registration No. 82,893
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W., Suite 900 East
Washington, D.C. 20001
Telephone: (202) 783-6040

Par Health Inc. Ex. 1002-0309

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**03/14/2025 04:10:12 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	69584978	AUTHORIZED BY	Sheena Wang
CUSTOMER #	6449	FILING DATE	07/11/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Sergio DUSCI

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 022135	**E20253DG11525332**	**Charles Pace**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1817	REQUEST FOR PRIORITIZED EXAMINATION	4515.00	1	4515.00
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	150.00	1	150.00
1801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	1500.00	1	1500.00
			TOTAL AMOUNT:	**$6,165.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

U.S. PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Inventor of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

Par Health Inc. Ex. 1002-0312

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

	1	Carlos L. Errando et al; "Letters to the Editor"; Regional Anesthesia and Pain Medicine; 23(3); 323-329; 1998 (1 page)	☐
	2	Lyvia Maria R. S. Gomes et al; "Neurotoxicity of Subarachnoid Preservative-Free S (+)-Ketamine in Dogs"; Pain Physician 2011; 14:83-90 (8 pages)	☐
	3	Beatriz Merchel Piovesan Pereira et al; "Benzalkonium Chlorides: Uses, Regulatory Status, and Microbial Resistance"; Applied and Environmental Microbiology; July 2019; Volume 85; Issue 13 (13 pages)	☐
	4	U.S. Department of Health and Human Services, FDA-2022-D-0219, Temporary Policies for Compounding Certain Parenteral Drug Products; Guidance for Industry, p. 12 (2024) (18 pages)	☐
	5	Jean-Marc Malinovsky et al; "Is Ketamine or It's Preservative Responsible for Neurotoxicity in the Rabbit?"; Anesthesiology; 78:109-115; 1993 (7 pages)	☐
	6	Huddy et al; "Preservative-free ketamine"; British journal of anaesthesia, 92(1), 152; 2004 (1 page)	☐
	7	Martin Stotz et al; "Histological Findings After Long-Term Infusion of Intrathecal Ketamine for Chronic Pain: A Case Report"; Journal of Pain and Symptom Management; Vol. 18 No. 3; September 1999; (6 pages)	☐
	8	D. A. H. de Beer et al; "Caudal additives in children-solutions or problems?"; British Journal of Anaesthesia; 90 (4): 487-98; 2003 (12 pages)	☐
	9	U.S. Department of Health and Human Services, FDA-2014-D-0779, Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, p. 44 (2020) (51 pages)	☐
	10	"<797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS"; The United States Pharmacopeial Convention; 2008 (61 pages)	☐

If you wish to add additional non-patent literature document citation information, please click the Add button Add

Par Health Inc. Ex. 1002-0313

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18770514
	Filing Date	2024-07-11
	First Named Inventor	Sergio DUSCI
	Art Unit	1627
	Examiner Name	SVETLANA M IVANOVA
	Attorney Docket Number	4830-114US2

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Par Health Inc. Ex. 1002-0314

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and the IDS Auto-Load Instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17(v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2025-03-14
Name/Print	Sheena X. Wang	Registration Number	82,893

Par Health Inc. Ex. 1002-0315

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Sergio DUSCI	Nonprovisional Application Number (if known):	18/770,514
Title of Invention:	READY-TO-USE KETAMINE PREMIX FORMULATION		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via USPTO patent electronic filing system.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via USPTO patent electronic filing system.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Sheena X. Wang/	Date March 14, 2025
Name (Print/Typed) Sheena X. Wang	Practitioner Registration Number 82,893

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;

2) a federal, state, local, or international agency, in response to its request;

3) a contractor of the USPTO having need for the information in order to perform a contract;

4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;

5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;

6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;

7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;

8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));

9) the Office of Personnel Management (OPM) for personnel research purposes; and

10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	: 18/770,514
1ST NAMED INVENTOR	: Sergio DUSCI
FILED	: July 11, 2024
ART UNIT	: 1627
EXAMINER	: SVETLANA M IVANOVA
CONFIRMATION NO.	: 2594
DOCKET NO.	: 4830-114US2
CUSTOMER NO.	: 6449

AMENDMENT WITH A REQUEST FOR CONTINUED EXAMINATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated December 19, 2024, please enter the following amendments and remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.
2. (Original) The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.
3. (Original) The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. (Currently Amended) The ketamine product of claim 1, wherein the aqueous ketamine solution is ~~preservative-free or~~ antimicrobial-free.
5. (Cancelled)
6. (Original) The ketamine product of claim 1, wherein the pH of the aqueous ketamine solution is about 3 to about 6.
7. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
8. (Original) The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
9. (Original) The ketamine product of claim 7, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
10. (Original) The ketamine product of claim 7, wherein the closure comprises a plastic material.

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11. (Original) The ketamine product of claim 7, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

12. (Original) The ketamine product of claim 10, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

13. (Previously Presented) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

14. (Original) The ketamine product of claim 7, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

15. (Previously Presented) The ketamine product of claim 7, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises polypropylene styrene-block copolymer.

16. (Original) The ketamine product of claim 7, wherein the infusion bag is contained within an overwrap.

17. (Original) The ketamine product of claim 16, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

18. (Original) The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

19. (Previously Presented) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

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20. (Original) The ketamine product of claim 19, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

21. (Cancelled)

22. (Cancelled)

23. (Original) The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

24. (Original) The ketamine product of claim 1, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months; and/or

the average number of particles equal to or greater than 25 μm does not exceed 600 per container following storage of the ketamine product at room temperature for 24 months.

25. (Previously Presented) The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ± 2°C / <25% RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ± 2°C/40%RH ± 5%RH is 97% or greater compared to the ketamine content before storage.

26. (Withdrawn) A method of preparing the ketamine product of claim 1, comprising:

i) preparing an aqueous solution comprising ketamine or a pharmaceutically acceptable salt thereof and water having a pH of about 3.5 to about 5.5;

ii) filtering the solution of step (i);

iii) filling the solution of step (ii) into an infusion bag; and

iv) terminally sterilizing the infusion bag of step (iii),

wherein the method further comprises overwrapping the infusion bag, wherein the overwrapping step comprises overwrapping the infusion bag of step (iii) prior to terminally sterilizing the infusion bag or overwrapping the terminally sterilized infusion bag of step (iv) with an overwrap.

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27. (Withdrawn) The method of claim 26, wherein the step of terminally sterilizing comprises autoclaving the infusion bag at a temperature between about 110 to about 130° C for a period of time of about 7 to about 60 minutes.

28. (Withdrawn) A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

29. (Currently Amended) A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C.

30. (Cancelled)

31. (Previously Presented) The ketamine product of claim 19, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

32. (Previously Presented) The ketamine product of claim 29, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at 25°C ± 2°C with relative humidity (RH) at 40% ± 5%.

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REMARKS

Claims 1-4, 6-20, 23-29, and 31-32 are pending. Claims 1, 4 and 29 have been amended. Claims 5, 21, 22 and 30 are cancelled. Claims 26-28 are withdrawn from consideration. Support for all amendments is found throughout the specification as filed and original claims 4, 19 and 30; and paragraphs [0009], [0014], [0044], [0045], [0057], [0058], [0059], [0112]-[114], Examples 1-5 and figures 1-4 and 7 of the specification. A total of 28 claims are pending. No new matter has been added.

The Applicant has not publicly dedicated or abandoned any unclaimed subject matter or acquiesced to any objection or rejection set forth in the Office Action. The Applicant expressly reserves the right to pursue prosecution of any presently or previously unelected, excluded, or cancelled claim embodiments, and/or species, in one or more future continuation and/or divisional applications.

In response to the Office Action, favorable reconsideration and allowance of the present application are respectfully requested.

For the reasons discussed below, it is submitted that this application is in condition for allowance.

Interview Summary

Applicant and Applicant's representative wish to thank Examiner Ivanova for the courtesies extended during the telephonic interview held on February 11, 2025. During the interview, Applicant's representative and the Examiner discussed the Office Action, the rejections under 35 U.S.C. § 102(a)(1) or in the alternative under 35 U.S.C. § 103 over Ketalar, and the rejection under 35 U.S.C. § 103 over Ketalar further in view of Conrad, and the proposed amendments to claims 1 and 29. The Examiner agreed that Ketalar, after dilution, does not have

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a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C and also that it comprises benzethonium chloride, which is known in the art to be a preservative and antimicrobial.

The Examiner also agreed that the proposed amendment to claims 1 and 29 to recite that the ketamine solution is preservative-free would overcome the anticipation rejection over Ketalar.

Regarding the obviousness rejections, the Examiner asserted that additional references may be found regarding preservative-free ketamine formulations. In response, Applicant's representative emphasized that the preservative free-ketamine product of the pending claims is a sterile and ready-to-use (RTU) product, comprises about 0.5 to about 2.5 mg/mL of ketamine, and has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C. The Examiner conducted a preliminary google search during the interview and mentioned several references. *See, e.g.*, Huddy, *et.al*, *Preservative-free ketamine*, 92 BRITISH J OF ANAESTHESIA 1, 152 (2004) (hereinafter "Huddy") and Malinovsky, et al., *Is ketamine or its preservative responsible for neurotoxicity in the rabbit?*, 78 ANESTHESIOLOGY 1, 109-115 (1993). The Applicant's representative and the Examiner briefly discussed the references that the Examiner found during the call, focusing on Huddy.

The Examiner asked the Applicant to conduct further due diligence regarding preservative-free ketamine formulations.

The Examiner stated that it was her impression that further search and consideration would be required to determine whether the amendment to claims 1 and 29 and the arguments discussed during the interview and detailed below would overcome the obviousness rejection over Ketalar. The Examiner agreed to focus the search on preservative-free, ready-to-use,

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ketamine products comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature.

Applicant now files this Response with a Request for Continued Examination to further address the Examiner's comments.

Response to Claim Rejections – 35 U.S.C. § 102(a)(1) Based on NDA016812 ("Ketalar")

Claims 1-6, 8, 18-20, 23-25, 29 and 31-32 were rejected under 35 U.S.C. § 102(a)(1) as allegedly being anticipated by Ketalar (ketamine hydrochloride) injection, for intravenous or intramuscular use, CIII, NDA016812, revised 6/2022 ("Ketalar"). Ketalar discloses preparing a ketamine product (vial or for infusion) for induction of anesthesia by diluting Ketalar with sterile water for injection, USP, normal saline, USP, or dextrose in water.

Applicant traverses this rejection because the cited art, considered alone or in combination, does not teach and would not have suggested all of the features of independent claims 1, 19 and 29 as currently amended. "To reject a claim as anticipated by a reference, the disclosure must teach every element required by the claim under its broadest reasonable interpretation." MPEP § 2131. Furthermore, the MPEP also requires the "consideration" of every claim feature in an obviousness determination. MPEP § 2143.03. To render independent claims 1, 19 and 29 unpatentable, Ketalar must **teach or suggest each and every claim feature**. *See In re Royka*, 490 F.2d 981 (CCPA 1974). Here, the diluted ketamine solution described in Ketalar does not teach or suggest at least the "preservative-free" and "wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C" limitations required by claims 1 and 29, as amended, and claim 19.

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On pages 3-4 of the Office Action, the Office asserts that "[s]ince Ketalar discloses a product with the same ingredients, it will also have the same osmolality, as per Applicant's claim 8, the same shelf life, as per Applicant's claims [1, and original cancelled claims] 21 and 22, the same chemical stability, as per Applicant's claim 23, the same average number of particles following storage of the ketamine product, as per Applicant's claim 24, the same ketamine content after accelerated storage, as per Applicant's claim 25, and the same shelf-life, as per Applicant's claim 30." Applicant respectfully disagrees as discussed further below. Additionally, independent claims 1, 19 and 29, as amended, state that "the ketamine solution is preservative-free." In contrast, Ketalar contains "not more than 0.10 mg/mL benzethonium chloride **added as a preservative** in water for injection." Ketalar at p. 10 (emphasis added). Thus, at least because Ketalar contains a preservative and the claims, as amended, require a solution that is preservative-free, the anticipation rejection has been rendered moot. Applicant respectfully requests withdrawal of the rejection.

Response to Claim Rejections – 35 U.S.C. § 103 Based on NDA016812 ("Ketalar")

Claims 1-6, 8, 18-20, 23-25, 29 and 31-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Ketalar. The Office Action acknowledges that **Ketalar requires dilution prior to use**. O.A. at p. 3. Furthermore, the Office Action acknowledges that the **Ketalar product needs to be used immediately after dilution**. *Id.* at 4.

On page 4, the Office Action explains various different interpretations of the claim limitation of "ready-to-use." It appears that the Office has overlooked that the specification sets forth an express definition as follows:

> As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which

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the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

MPEP 2111.01(IV)(A) states that "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim." Thus, the Office Action's various different interpretations are unnecessary and irrelevant where the only definition that controls is the one that is expressly provided in the specification. *Id.*

Applicant traverses the rejection because Ketalar does not teach and would not have suggested all of the features of claims 1, 19 and 29, from which claims 2-6, 8, 18, 20, 23-25 and 31-32 depend.

First, Ketalar only teaches a concentrated ketamine product that must be diluted prior to use and used immediately after dilution. Ketalar does not disclose and would not have suggested the claimed product that is a ready-to-use product comprising a ketamine solution having about 0.5 to about 2.5 mg/mL of ketamine, wherein the ketamine solution is preservative-free, and wherein the ketamine product has a shelf-life of more than six months under the specified conditions. Applicant submits that a person of ordinary skill in the art would understand that a preservative-free formulation would have different shelf-life, chemical stability, average number of particles following storage, and/or ketamine content after accelerated storage characteristics compared to a formulation with preservatives, such as Ketalar. Furthermore, a person of ordinary skill in the art would not expect a preservative-free formulation to have increased shelf-life compared to a formulation containing a preservative such as Ketalar.

Additionally, a person of ordinary skill would recognize that Ketalar is not, and does not suggest, a ketamine product comprising an aqueous ketamine solution **comprising about 0.5**

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to about 2.5 mg/mL ketamine, wherein the ketamine product **is sterile** and **ready-to-use (RTU)**, and **has a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C**. Ketalar describes a concentrated ketamine solution that would not inherently have the same shelf-life as the ketamine product of claims 1-6, 8, 18-20, 23-25, 29 and 31-32 **after dilution**. Indeed, as discussed below, the claimed shelf life also would not have been obvious for the sterile, low-concentration ready-to-use solutions claimed. The Ketalar label specifies that a physician should "not administer the 100 mg/mL concentration of KETALAR intravenously without proper dilution… [and m]ust be **used immediately after dilution.**" Ketalar at p. 2 (emphasis added). Therefore, Ketalar does not teach a ready-to-use[1] product comprising a ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine that also has "a shelf-life of more than six months when stored at a controlled room temperature between 15–30°C" of amended independent claims 1 and 29 and independent claim 19 because it has to be used immediately.

Second, a person skilled in the art of injectable formulation development would not look to Ketalar, a concentrated product that requires admixing or compounding before use, to arrive at the low concentration and ready-to-use (RTU) solutions having the shelf-life or stability characteristics of the instant invention. There is lack of scientific comparability between admixed or compounded drugs, on the one hand, and sterile, ready-to-use injection products on the other hand. *First*, Ketalar only teaches to dilute the formulation immediately prior to use. It does not teach that the product should be prepared at a registered compounding pharmacy or

[1] Again, the specification defines the term as follows: As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

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that it should be sterilized following dilution. *Second*, Ketalar contains a preservative. *Third*, as explained by the FDA, even if drug products are compounded at a registered outsourcing facility and terminally sterilized (which Ketalar does not teach or suggest), the expiration date of compounded drug products that do not contain preservatives, but are terminally sterilized by the compounding facility, should be **at most 14 days** after release at room temperature when sterility testing is not completed, and **not more than 28 days** beyond the completion of a sterility test when one is completed. *See* DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA-2022-D-0219, TEMPORARY POLICIES FOR COMPOUNDING CERTAIN PARENTERAL DRUG PRODUCTS; GUIDANCE FOR INDUSTRY, at 12 (2024) (hereinafter "FDA Policies 2024"); *see also* DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA-2014-D-0779, CURRENT GOOD MANUFACTURING PRACTICE—GUIDANCE FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FD&C ACT, at 44 (2020) (hereinafter "FDA Interim Guidance"). As illustrated by the FDA Interim Guidance (which was in effect at the priority date), drug compounding manufacturers do not necessarily terminally sterilize or complete stability or sterility testing on their products before the product is released. *See* FDA Interim Guidance at 44 (identifying acceptable beyond use dates (BUD) under various circumstances).

Furthermore, Ketalar does not instruct the user to sterilize the diluted solution or complete stability or sterility testing before use. Terminal sterilization techniques, such as autoclaving, subject the product to rigorous conditions (e.g., high temperature) that may degrade the product, and may have different and unpredictable effects depending on the particular active ingredient, the excipients, the container system, and the combination thereof. The cited art does not provide any information regarding terminal sterilization of a ketamine product, and in

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particular does not provide information regarding terminal sterilization or autoclaving of a ketamine product containing 0.5 to 2.5 mg/mL ketamine as required by claims 2 and 18-20.

Furthermore, as explained by the United States Pharmacopeia, Chapter ⟨797⟩ Pharmaceutical Compounding—Sterile Preparations (USP Revision Bulletin, 2008) ("USP"):

> When attempting to predict a theoretical BUD [beyond-use date], a compounded or ***admixed preparation should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components***. For example, antioxidant, buffering, or antimicrobial properties of a sterile vial for injection (SVI) might be lost upon its dilution, with the potential of seriously compromising the chemical stability of the SVI's active ingredient or the physical or microbiological stability of the SVI formulation in general. ***Thus, the properties stabilized in the SVI formulation usually cannot be expected to be carried over to the compounded or admixed preparation***.

See USP at 41 (emphasis added).

Therefore, admixed and compounded products are well known to lack the same stability as the sterile and ready-to-use (RTU) products recited in amended independent claims 1 and 29 and independent claim 19. There is no evidence that the Ketalar product referenced in the Office Action, after dilution to the ketamine concentration of the recited claims, would meet either the sterility or the stability requirements identified in the recited claims. And if one were to dilute it, then it would not meet the definition of "ready-to-use" as required by the claims where the applicant has acted as its own lexicographer to provide the controlling definition: As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the

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product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration). *See* MPEP 2111.01(IV)(A).

Ketalar does not provide a person of ordinary skill with any guidance, suggestion, or motivation to prepare the claimed **sterile, ready-to-use, preservative-free** ketamine composition **comprising about 0.5 to about 2.5 mg/mL ketamine** that **can be stored for at least six months when stored at a controlled room temperature between 15–30°C**. In fact, Ketalar repeatedly notes that the diluted ketamine solution must immediately be administered to the subject and is **not** suitable for prolonged storage. And the Office's reliance on a dilution step means that the proposed modification to the prior art results in something that does not meet the definition of ready-to-use required by the claims.

Third, Applicant also submits that the claimed ready-to-use premix composition provides for surprising and unexpected advantages over the concentrated compositions in the cited art. For example, the claimed preservative-free RTU ketamine composition provides advantages in the ability to be stored over prolonged periods of time while maintaining stability at low, ready-to-use concentrations of ketamine. For example, Example 3 of the instant application studied the long term and accelerated stability of diluted, commercially-available, preservative-containing ketamine solutions compared to the preservative-free ketamine product of the instant application and concluded that "Tables 6-9 surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride under accelerated conditions and long-term storage." *See* Application No. 18/77,514 at [0114]. Such advantages over the concentrated multiple-dose vial compositions of the prior art are

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further evidence of the non-obviousness of the claims over the cited references. *See* M.P.E.P. § 716.02(a).

Thus, the prior art does not teach all of the elements of the claimed invention. Indeed, the prior art specifically teaches away from storing a diluted ketamine solution at room temperature for prolonged periods (e.g., at least six months as required by all pending claims, or twenty-four months as recited in dependent claims 23, 31, and 32). Furthermore, Applicant respectfully submits that the disclosures in Ketalar fail to provide reasonable guidance that would have motivated a skilled artisan to modify Ketalar, as alleged, with a reasonable expectation of success to achieve the claimed invention. Thus, the claimed invention is not rendered obvious by the teachings of Ketalar.

All remaining claims under consideration (claims 2-20, 23-25, and 31-32) are dependent from one of claims 1, 19, or 29, and are therefore nonobvious for at least the same reasons. Therefore, Applicant respectfully requests that the rejections be withdrawn for at least these reasons.

Response to Prior Art Discussed During Examiner Interview– Concentrated preservative-free ketamine does not render obvious the pending claims

In response to the internet search for mentions of preservative-free ketamine compositions that the Examiner conducted during the telephonic interview held on February 11, 2025, Applicant first notes that there is only one FDA approved injectable pharmaceutical drug product containing ketamine hydrochloride (New Drug Application (NDA) number 016812), which is packaged in 10 mg/ml, 50 mg/ml or 100 mg/ml multi-dose vials, which requires dilution before use, must be used immediately following dilution, and contains the preservative benzethonium chloride. *See* Ketalar (ketamine hydrochloride) injection, for intravenous or

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intramuscular use, CIII, NDA016812, at 1,2 and 10, (2022). The Ketalar formulation is different for multiple reasons explained above from the claimed preservative-free, sterile and ready-to-use (RTU) ketamine product. Additionally, there is currently no FDA-approved sterile and ready-to-use (RTU) ketamine solution, either with or without a preservative.

In response to the Examiner's request to conduct further due diligence on preservative-free ketamine compositions, Applicant has identified certain scientific journal articles discussing preservative-free ketamine, none of which describes a ketamine product that meets the limitations of the pending claims. *See, e.g.*, Errando, et al., *Some misleadings about ketamine and their preservatives/Response*, 23 *Regional Anesthesia and Pain Medicine* 3, 323 (1998) (hereinafter "Errando"); and Gomes, *et al.*, *Neurotoxicity of subarachnoid preservative-free S (+)-ketamine in dogs*, 14 PAIN PHYSICIAN 1, 83 (2011) (hereinafter "Gomes"). The preservative-free ketamine used in Gomes was **packaged in a 50 mg/ml ampoule** and diluted in saline prior to intrathecal application. *See* Gomes at 84-85. Huddy and Errando were letters to the editor and did not describe the method of their referenced studies in detail. The studies that Huddy and Errando referenced include (1) De Beer, et al., *Caudal additives in children—solutions or problems*?, 90 BRITISH J. OF ANAESTHESIA 4, 487-498 (2003); (2) Stotz, et al., *Histological findings after long-term infusion of intrathecal ketamine for chronic pain: a case report*, 18 J. OF PAIN AND SYMPTOM MANAGEMENT 3, 223-228 (1999); and (3) Malinovsky, et al., *Is ketamine or its preservative responsible for neurotoxicity in the rabbit?*, 78 ANESTHESIOLOGY 1, 109-115 (1993). The preservative-free ketamine used in each of these studies was **packaged in a concentrated form** then diluted with saline or distilled water prior to use. Nothing in the references indicates that the diluted preservative-free ketamine was stored for any length of time prior to use or that it was sterile following dilution. *Id.* Thus, none of these publications relates to

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a sterile and ready-to-use (RTU) ketamine product comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature.

As explained above with respect to Ketalar, the concentrated preservative-free ketamine formulations referenced in the prior art do not teach, suggest, or render obvious a sterile, RTU preservative-free ketamine formulation, comprising about 0.5 to about 2.5 mg/mL ketamine with a shelf-life of more than six months when stored at a controlled room temperature. A person of ordinary skill in the art would not expect a diluted formulation to have the same stability characteristics of a concentrated formulation, even if it contains the same components. *See* USP at 41; FDA Policies 2024 at 12.

In response to the Examiner's request to clarify the role of benzethonium chloride in a ketamine product, such as Ketalar, Applicant submits that it is known in the art that benzethonium chloride is a preservative and an antimicrobial that has "broad-spectrum antimicrobial properties against bacteria, fungi, and viruses." Merchel Piovesan Pereira, *et. al.*, *Benzalkonium chlorides: uses, regulatory status, and microbial resistance*, 85 APPLIED AND ENVIRONMENTAL MICROBIOLOGY 13, at 1 (2019). As noted above, Ketalar refers to benzethonium chloride as a preservative.

Response to Claim Rejections – 35 U.S.C. § 103 Based on Ketalar and Conrad

Claims 7 and 9-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ketalar further in view of US 11,207,309 B2 to Conrad *et al.* ("Conrad"). The Office notes that Ketalar is discussed in the above section and acknowledges that it does not disclose the characteristics of the infusion bag of claims 7 and 9-17. O.A. at p. 6. The Office further acknowledges that Conrad relates to parenteral liquid formulations of **fentanyl**. O.A. at p. 8. However, the Office notes that this fentanyl product is supplied as a terminally sterilized ready-to-administer product in an

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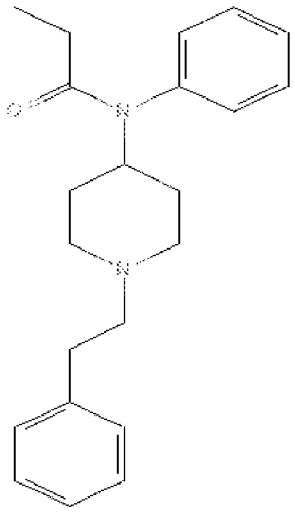
infusion container that has the characteristics of claims 7 and 9-17, including the twist-off closure and aluminum overpouch. *Id.* at 9-10.

First, amended independent claim 1 is not anticipated or rendered obvious by Ketalar. Conrad is only cited as allegedly disclosing stable fentanyl formulations supplied as a ready-to-administer product in an infusion container or bag and is not alleged to and does not remedy the deficiencies of Ketalar. Claims 7 and 9-17 depend directly or indirectly on independent claim 1. Thus, Applicant respectfully requests withdrawal of the rejection of claims 7 and 9-17.

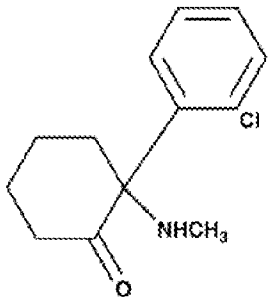
Second, Conrad relates to stable **fentanyl** formulations and does not remedy the deficiencies of Ketalar because Ketalar is directed to a different active ingredient, **ketamine**. The Office ignores the art-recognized difficulties in creating stable ready to use formulations of specific drugs, accounting for each drug's chemical properties, specific excipients in the formulation, and selection of drug containers. "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353, 1359 (Fed. Cir. 2008) (quoting *KSR,* 550 U.S. at 420).

Fentanyl is chemically known as N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propenamide and has the chemical structure shown below:

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In contrast, ketamine is known as (±)-2-(*o*-Chlorophenyl)-2-(methylamino)cyclohexanone and has the chemical structure shown below:



A person of ordinary skill in the art would understand that fentanyl and ketamine would be expected to have different degradation pathways and to react chemically differently with excipients and infusion containers. A person of ordinary skill in the art would understand that a formulator must consider physical stability, chemical stability, and microbiological stability in light of all of the components in a formulation, including the potential leachables and extractables associated with the packaging materials. Drug products comprising ketamine and fentanyl are complex systems that include numerous chemical species co-existing in a range of interdependent equilibrium processes, which may be affected by the interaction of the drug components and with potential leachables and extractables associated with the packaging

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materials. In addition to the chemical differences of the active ingredient, the excipients included in the formulation of independent claim 1 and Conrad are different. For example, the Conrad formulation comprises about 0.5 mg/mL to about 5 mg/mL of a buffer. *See* Conrad at claim 1. In contrast to Conrad, the invention of independent claim 1 does not require buffer excipients. A person of ordinary skill in the art would understand that the presence of a buffer may affect the stability characteristics and packaging materials considerations for a ready to use (RTU) drug product. For at least this additional reason, Applicant respectfully requests withdrawal of the rejection of claims 7 and 9-17.

Accordingly, Applicant respectfully submits that the rejections of record should be withdrawn for at least the foregoing reasons.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections, and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

If any fees are required, such as, but not limited to, any extension of time fee under 37 C.F.R. 1.17, Applicant hereby petitions for an extension of time, if necessary, and authorizes the Office to charge all required fees to deposit account number 02-2135.

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Respectfully submitted,

By: /Sheena X. Wang/

Sheena X. Wang
Attorney for Applicant
Registration No. 82,893
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.,
Suite 900 East
Washington, D.C. 20001
Telephone: (202) 783-6040
Facsimile: (202) 783-6031

Par Health Inc. Ex. 1002-0340

Examiner-Initiated Interview Summary	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio		
	Examiner SVETLANA M IVANOVA	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
SVETLANA M IVANOVA	Primary Examiner	Telephonic
SHEENA WANG	Attorney of Record	

Date of Interview: 19 March 2025

Issues Discussed:

Proposed Amendment(s)

The Examiner called and indicated that the application would be in a condition for an allowance, if Applicant agreed to claim amendments, as reflected in full in the attached Examiner's amendment. After consulting with the client, Applicant called back on March 20, and indicated that Applicant agrees. Emails were also exchanged on attempting to establish communication (attached), but all agreements were made by phone.

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Par Health Inc. Ex. 1002-0341

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

CPC - Searched*		
Symbol	Date	Examiner
A61K31/135	10/18/2024	si

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Filing receipt review	10/18/2024	si
DAV inventor search	10/18/2024	si
PE2E assignee search	10/18/2024	si
PE2E (attached)	10/18/2024	si
Google (attached)	10/18/2024	si
PE2E (ketamine and (aqueous or solution)).clm.	12/13/2024	si
Google (ketalar, ketamine, ready to use)	12/13/2024	si
Google (ketamine preservative-free, various)	03/20/2025	si
PE2E (L13-L15)	03/20/2025	si

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Par Health Inc. Ex. 1002-0342

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	**Art Unit**
	SVETLANA M IVANOVA	1627

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K	31/135	03/20/2025	si

/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	

Par Health Inc. Ex. 1002-0343

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	**Art Unit**
	SVETLANA M IVANOVA	1627

CPC						
Symbol					**Type**	**Version**
A61K	/	31	/	135	F	2013-01-01
A61M	/	5	/	14	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
A61M	/	2005	/	1401	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	23	
/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627	20 March 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	one	none

U.S. Patent and Trademark Office

Part of Paper No.: 20250320

Par Health Inc. Ex. 1002-0344

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	**Art Unit**
	SVETLANA M IVANOVA	1627

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	135

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 23	
/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627 (Primary Examiner) 20 March 2025 (Date)	O.G. Print Claim(s) one	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No.: 20250320

Par Health Inc. Ex. 1002-0345

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/770,514	DUSCI, Sergio
	Examiner	**Art Unit**
	SVETLANA M IVANOVA	1627

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	7	10	16	19	20	28								
2	2	8	11	17	20	21	29								
3	3	9	12		21		30								
	4	10	13		22	22	31								
	5	11	14	18	23	23	32								
	6	12	15		24										
4	7	13	16	19	25										
5	8	14	17		26										
6	9	15	18		27										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23	
/SVETLANA M IVANOVA/ Primary Examiner, Art Unit 1627 (Primary Examiner)	20 March 2025 (Date)	O.G. Print Claim(s) one	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20250320

Par Health Inc. Ex. 1002-0346

Ivanova, Svetlana M.

From: Sheena Wang <swang@rothwellfigg.com>
Sent: Thursday, March 20, 2025 8:59 AM
To: Ivanova, Svetlana M.
Subject: RE: U.S. App. No. 18/770,514

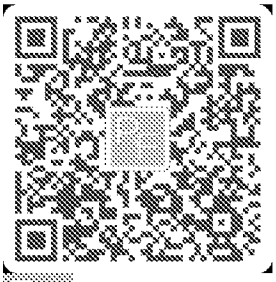
CAUTION: This email has originated from a source outside of USPTO. **PLEASE CONSIDER THE SOURCE** before responding, clicking on links, or opening attachments.

Good morning Ms. Ivanova,

Thank you for your time yesterday, I tried to call you this morning and left a voicemail. Please call me back at your convenience. I will also try to call you again later today.

Thanks,
Sheena

Sheena X. Wang (she/her/hers)
Associate
Rothwell, Figg, Ernst & Manbeck, P.C.
901 New York Avenue, NW
Suite 900 East
Washington, DC 20001
Phone: 202-783-6040
Fax: 202-783-6031



ROTHWELL FIGG

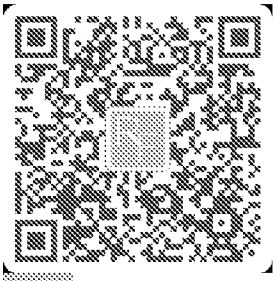
From: Sheena Wang
Sent: Wednesday, March 19, 2025 10:08 AM
To: Ivanova, Svetlana M. <Svetlana.Ivanova@USPTO.GOV>
Subject: RE: U.S. App. No. 18/770,514

Dear Ms. Ivanova,

Thank you for your email below. I tried to call you this morning and left a voicemail. Please call me back at your convenience. I will also try to call you again later today.

Thank you,

Sheena X. Wang (she/her/hers)
Associate
Rothwell, Figg, Ernst & Manbeck, P.C.
901 New York Avenue, NW
Suite 900 East
Washington, DC 20001
Phone: 202-783-6040
Fax: 202-783-6031



ROTHWELL FIGG

From: Ivanova, Svetlana M. <Svetlana.Ivanova@USPTO.GOV>
Sent: Tuesday, March 18, 2025 11:35 PM
To: Sheena Wang <swang@rothwellfigg.com>
Subject: U.S. App. No. 18/770,514

Dear Ms. Wang:

I would like to discuss a proposal for an Examiner's amendment. Could you give me a phone call back at your convenience tomorrow, please?

Thank you.
Svetlana Ivanova

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	40	"5439643"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:16 PM
L2	19	"8617467"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:21 PM
L3	75006	A61K31/135	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:24 PM
L4	45591	A61K31/135.ipcr,cpc.	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/16 11:24 PM
L5	17	"11207309"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2024/10/17 10:11 PM
L6	4	((("INFORLIFE") near3 ("SA"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:28 PM
L7	331	(ketamine AND (solution OR aqueous)).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM
L8	438397	infusion	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM
L9	104	L7 AND L8	(US-PGPUB; USPAT)	OR	ON	ON	2024/10/18 12:31 PM
L10	332	(ketamine AND (solution OR aqueous)).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2024/12/13 09:45 PM
L11	1	"20250025431"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/02/11 03:40 PM
L12	2	"20250025431"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/03/18 11:36 PM
L13	404	(ketamine AND (solution OR aqueous)).clm.	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/03/20 03:41 PM
L14	7773	"preservative-free" OR "anti-microbial free"	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/03/20 03:42 PM
L15	12	L13 AND L14	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/03/20 03:42 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp

N1	8445	A61K31/135	(US-PGPUB; USPAT)	OR	ON	ON	2025/03/19 10:36 AM

PTO/SB/08a (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

U.S. PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Inventor of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S. PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Inventor or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

Par Health Inc. Ex. 1002-0351

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

	1	Carlos L. Errando et al; "Letters to the Editor"; Regional Anesthesia and Pain Medicine; 23(3); 323-329; 1998 (1 page)	☐
	2	Lyvia Maria R. S. Gomes et al; "Neurotoxicity of Subarachnoid Preservative-Free S (+)-Ketamine in Dogs"; Pain Physician 2011; 14:83-90 (8 pages)	☐
	3	Beatriz Merchel Piovesan Pereira et al; "Benzalkonium Chlorides: Uses, Regulatory Status, and Microbial Resistance"; Applied and Environmental Microbiology; July 2019; Volume 85; Issue 13 (13 pages)	☐
	4	U.S. Department of Health and Human Services, FDA-2022-D-0219, Temporary Policies for Compounding Certain Parenteral Drug Products; Guidance for Industry, p. 12 (2024) (18 pages)	☐
	5	Jean-Marc Malinovsky et al; "Is Ketamine or It's Preservative Responsible for Neurotoxicity in the Rabbit?"; Anesthesiology; 78:109-115; 1993 (7 pages)	☐
	6	Huddy et al; "Preservative-free ketamine"; British journal of anaesthesia, 92(1), 152; 2004 (1 page)	☐
	7	Martin Stotz et al; "Histological Findings After Long-Term Infusion of Intrathecal Ketamine for Chronic Pain: A Case Report"; Journal of Pain and Symptom Management; Vol. 18 No. 3; September 1999; (6 pages)	☐
	8	D. A. H. de Beer et al; "Caudal additives in children-solutions or problems?"; British Journal of Anaesthesia; 90 (4): 487-98; 2003 (12 pages)	☐
	9	U.S. Department of Health and Human Services, FDA-2014-D-0779, Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, p. 44 (2020) (51 pages)	☐
	10	"<797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS"; The United States Pharmacopeial Convention; 2008 (61 pages)	☐

If you wish to add additional non-patent literature document citation information, please click the Add button Add

Par Health Inc. Ex. 1002-0352

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

EXAMINER SIGNATURE			
Examiner Signature	/SVETLANA M IVANOVA/	Date Considered	03/18/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Par Health Inc. Ex. 1002-0353

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and the IDS Auto-Load Instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17(v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Sheena X. Wang/	Date (YYYY-MM-DD)	2025-03-14
Name/Print	Sheena X. Wang	Registration Number	82,893

Par Health Inc. Ex. 1002-0354

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18770514
Filing Date	2024-07-11
First Named Inventor	Sergio DUSCI
Art Unit	1627
Examiner Name	SVETLANA M IVANOVA
Attorney Docket Number	4830-114US2

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Par Health Inc. Ex. 1002-0355

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.I/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

6449 7590 03/27/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 03/27/2025

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

TITLE OF INVENTION: READY-TO-USE KETAMINE PREMIX FORMULATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	06/27/2025

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Par Health Inc. Ex. 1002-0357

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

6449 7590 03/27/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

TITLE OF INVENTION: READY-TO-USE KETAMINE PREMIX FORMULATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	06/27/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
IVANOVA, SVETLANA M	1627	514-649000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Par Health Inc. Ex. 1002-0358

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 03/27/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER	
IVANOVA, SVETLANA M	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 03/27/2025

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Par Health Inc. Ex. 1002-0359

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/770,514	Applicant(s) DUSCI, Sergio	
	Examiner SVETLANA M IVANOVA	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 3/14/2025.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SVETLANA M IVANOVA/
Primary Examiner, Art Unit 1627

Par Health Inc. Ex. 1002-0361

Continuation of 3. The allowed claim(s) is/are: 1-3,7-20,23,25,28-29 and 31-32

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Allowable Subject Matter

Claims 1-3, 7-20, 23, 25, 28, 29, 31 and 32 are allowed.

The following is an examiner's statement of reasons for allowance. Applicant has amended the claims to recite "wherein the ketamine solution is preservative-free". Applicant has further agreed to amend the claims to recite the wherein limitation of claim 4 "wherein the ketamine solution is antimicrobial-free". This removes any potential ambiguity since compounds, such as benzethonium chloride are classified as both preservative and antimicrobial agents. Applicant further agreed to amend the independent claims with the pH limitation of about 3.5 to about 5.5 consistent with Applicant's data of its tested formulations in the specification. Applicant further agreed to cancel some further claims, as indicated below, and to some further claim amendments to overcome some minor claim issues.

With respect to the "wherein the ketamine solution is preservative-free" the Examiner notes that the prior art discloses motivation to prepare a ketamine solution, which is preservative-free. Motivation to do so is found, for instance, in Malinovsky et al., Is ketamine or its preservative responsible for neurotoxicity in the rabbit?, Anesthesiology, 1993 Jan;78(1):109-15 ("Malinovsky, or record). Malinovksy discloses,

inter alia: "Background: Although ketamine has been administered spinally in humans, previous neurotoxicity studies have shown that it can induce spinal cord lesions in various animal models. The aim of this work was to evaluate by histologic and blood-brain barrier studies whether different components of the commercial ketamine solution might be responsible for the microscopic lesions observed. . . Results: Isomers of ketamine did not induce spinal cord lesions in either study, but chlorobutanol (the preservative used in the ketamine solution) induced significant severe spinal cord lesions in both studies. Conclusions: The appearance of spinal cord lesions after intrathecal chlorobutanol strongly suggests that this preservative is responsible for apparent toxicity of ketamine and therefore should not be used in any solution intrathecally injected into humans." (Abstract). Further motivation to do so is found, for instance, in de Beer, Caudal additives in children—solutions or problems?, British Journal of Anaesthesia, Volume 90, Issue 4, April 2003, Pages 487-498 ("de Beer", of record), which discloses, *inter alia*: "More recently, spinal neurotoxicity has been reported in a patient with chronic pain after the long-term infusion of intrathecal ketamine.91 In this case, the addition of ketamine with preservative (benzethonium chloride) to a mixture of bupivacaine, morphine and clonidine resulted in isolated lymphocytic vasculitis of the spinal cord and leptomeninges, without any clinical signs of neurological deficit. However, despite numerous studies, the causes of neurotoxicity remain controversial. While some investigators blame the preservative (benzethonium chloride or chlorbutanol),66 others claim that benzethonium chloride is not toxic in primates.11 Although the addition of ketamine to local anaesthetic solutions has been shown to significantly prolong the duration of caudal analgesia in children,16 45 58 74

87 the practice has not been adopted widely in the UK. This may be partly because of the difficulty in obtaining preservative-free ketamine (Ketamine Curamed®), which is not available in the UK. The commercially available preparation (Ketalar®) should not be administered epidurally because of the risk of neurotoxicity from the preservative agent (benzethonium chloride in the UK)."

What the prior art does not disclose, however, is how to prepare one such preservative-free formulation, which is ready-to-use and stable over time. To this end, the commercially available preparation (Ketalar®) has the preservative benzethonium chloride. Applicant was able to develop and test as suitable a preservative-free formulation, which is ready-to-use and stable over time.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Sheena Wang on March 20, 2025.

-Re-write the claims as follows:

-1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the ketamine product is sterile and ready-to-use (RTU), wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15—30°C.

-19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, ~~and~~ wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15—30°C.

-In claim 24, line 2, insert –of-- between “24 months” and “storage”.

-29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free,

wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15—30°C.

-In claim 31, line 2, insert –of-- between “24 months” and “storage”.

-In claim 32, line 2, insert –of-- between “24 months” and “storage”.

-Cancel claims 4, 6, 24, 26 and 27.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SVETLANA M IVANOVA whose telephone number is (571)270-3277. The examiner can normally be reached 8:30-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SVETLANA M IVANOVA/
Primary Examiner, Art Unit 1627

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

6449 7590 04/01/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
04/01/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Par Health Inc. Ex. 1002-0369

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/770,514	**Applicant(s)** DUSCI, Sergio	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 14 March 2025 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☑ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

Par Health Inc. Ex. 1002-0370

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**06/23/2025 04:12:07 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
PATENT CENTER #	71016589	AUTHORIZED BY	Sheena Wang
CUSTOMER #	6449	FILING DATE	07/11/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Sergio DUSCI

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 022135	**E20256MG12589888**	**Charles Pace**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1501	UTILITY ISSUE FEE	1290.00	1	1290.00
			TOTAL AMOUNT:	**$1,290.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Par Health Inc. Ex. 1002-0371

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/770,514	**06/23/2025 04:12:07 PM Z ET**	**4830-114US2**

Title of Invention

READY-TO-USE KETAMINE PREMIX FORMULATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2594	FILED BY	Charles Pace
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CUSTOMER #	6449	FIRST NAMED INVENTOR	Sergio DUSCI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Sheena Wang

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
4830-0114US2 Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	406 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
4830-0114US2 Issue Fee Transmittal.pdf	E207ED9DB53F865FC84CC473795AC78D95A5D183A92A94E26B225476AF4CC38205483AAF3F8F7C0F757798B336864DB7BD4C5C415940D1967D3766386D47C45D

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

6449 7590 03/27/2025
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/11/2024	Sergio DUSCI	4830-114US2	2594

TITLE OF INVENTION: READY-TO-USE KETAMINE PREMIX FORMULATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	06/27/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
IVANOVA, SVETLANA M	1627	514-649000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Rothwell, Figg, Ernst & Manbeck, P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: INFORLIFE SA

(B) RESIDENCE: (CITY and STATE OR COUNTRY): CAMPASCIO, SWITZERLAND

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 02-2135

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Sheena X. Wang/ Date 6/20/2025

Typed or printed name Sheena X. Wang Registration No. 82,893

Par Health Inc. Ex. 1002-0375

-Re-write the claims as follows:

-1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the ketamine product is sterile and ready-to-use (RTU), wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15—30°C.

-19. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, ~~and~~ wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15—30°C.

Change(s) applied to document, /G.M./ 4/13/2025

-In ~~claim 24~~ claim 23, line 2, insert –of-- between “24 months” and “storage”.

-29. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free,

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/770,514	07/29/2025	12370153	4830-114US2	2594

6449 7590 07/16/2025

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

Par Health Inc. Ex. 1002-0377

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Sergio DUSCI, Tresivio, ITALY;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

INFORLIFE SA, CAMPASCIO, SWITZERLAND;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Par Health Inc. Ex. 1002-0378

United States of America

To Promote the Progress of Science and Useful Arts

The Director

of the United States Patent and Trademark Office has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this United States

Patent

grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

Acting Director of the United States Patent and Trademark Office

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Maintenance Fee Notice

If the application for this patent was filed on or after December 12, 1980, maintenance fees are due three years and six months, seven years and six months, and eleven years and six months after the date of this grant, or within a grace period of six months thereafter upon payment of a surcharge as provided by law. The amount, number and timing of the maintenance fees required may be changed by law or regulation. Unless payment of the applicable maintenance fee is received in the United States Patent and Trademark Office on or before the date the fee is due or within a grace period of six months thereafter, the patent will expire as of the end of such grace period.

Patent Term Notice

If the application for this patent was filed on or after June 8, 1995, the term of this patent begins on the date on which this patent issues and ends twenty years from the filing date of the application or, if the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, 365(c), or 386(c), twenty years from the filing date of the earliest such application ("the twenty-year term"), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b), and any extension as provided by 35 U.S.C. 154(b) or 156 or any disclaimer under 35 U.S.C. 253.

If this application was filed prior to June 8, 1995, the term of this patent begins on the date on which this patent issues and ends on the later of seventeen years from the date of the grant of this patent or the twenty-year term set forth above for patents resulting from applications filed on or after June 8, 1995, subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b) and any extension as provided by 35 U.S.C. 156 or any disclaimer under 35 U.S.C. 253.

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US012370153B2

(12) **United States Patent**
Dusci

(10) **Patent No.: US 12,370,153 B2**
(45) **Date of Patent: Jul. 29, 2025**

(54) **READY-TO-USE KETAMINE PREMIX FORMULATION**

(71) Applicant: **INFORLIFE SA**, Campascio (CH)

(72) Inventor: **Sergio Dusci**, Tresivio (IT)

(73) Assignee: **INFORLIFE SA**, Campascio (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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Related U.S. Application Data

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A61K 31/135 (2006.01)
A61K 45/06 (2006.01)
A61M 5/14 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/135*** (2013.01); ***A61K 45/06*** (2013.01); ***A61M 5/14*** (2013.01); *A61M 2005/1401* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/135
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to a sterile, ready-to-use, stable aqueous solution of ketamine suitable for direct intravenous infusion to a patient in need thereof, wherein the composition is disposed within a sealed infusion container as a premixture. The invention further relates to aqueous solutions of ketamine that are free of antimicrobials such as benzethonium chloride and are shelf-stable. The pharmaceutical compositions can be used, for example, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.

23 Claims, 8 Drawing Sheets

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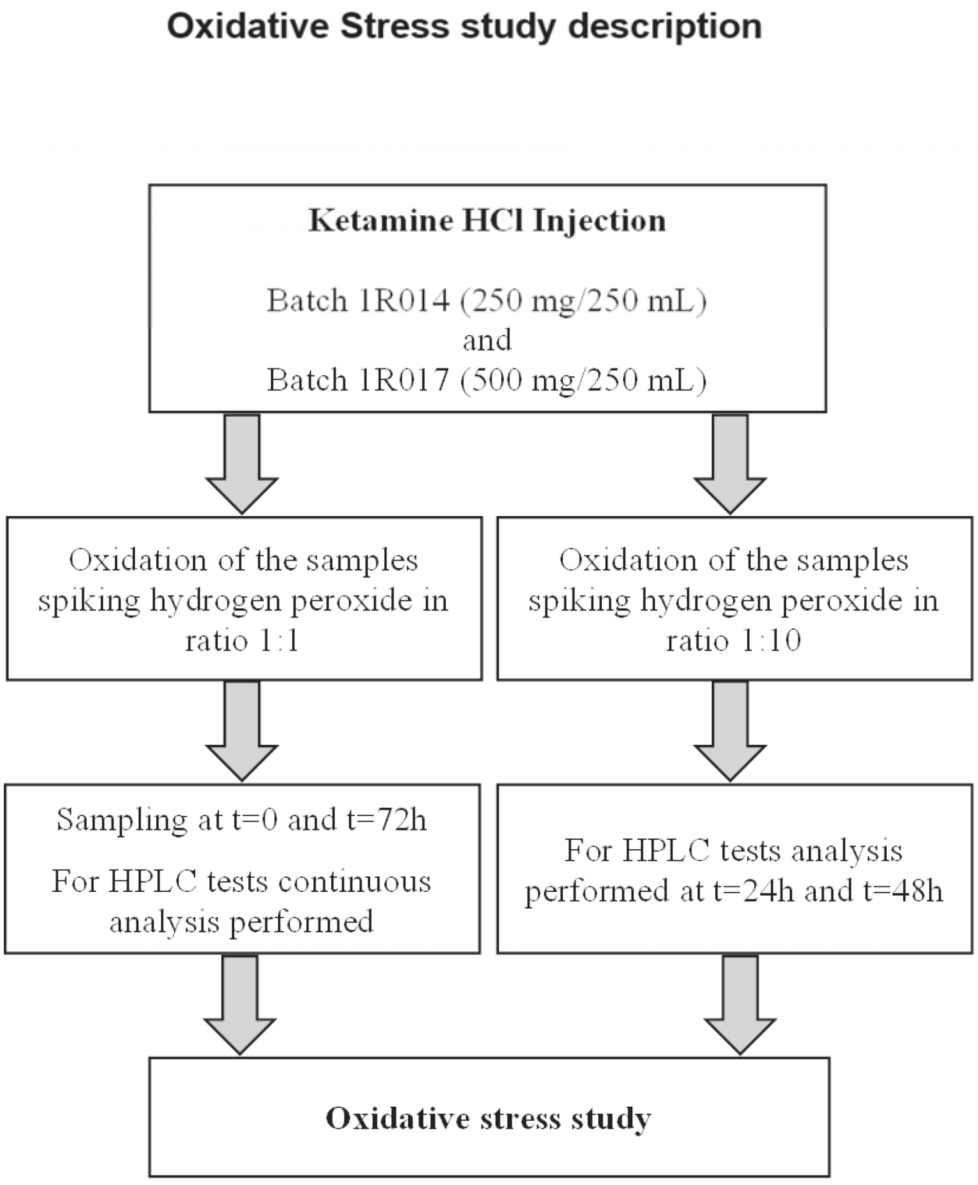

Oxidative Stress study description
Ketamine HCl Injection
Batch 1R014 (250 mg/250 mL)
and
Batch 1R017 (500 mg/250 mL)
Oxidation of the samples spiking hydrogen peroxide in ratio 1:1
Oxidation of the samples spiking hydrogen peroxide in ratio 1:10
Sampling at t=0 and t=72h
For HPLC tests continuous analysis performed
For HPLC tests analysis performed at t=24h and t=48h
Oxidative stress study

Fig. 1

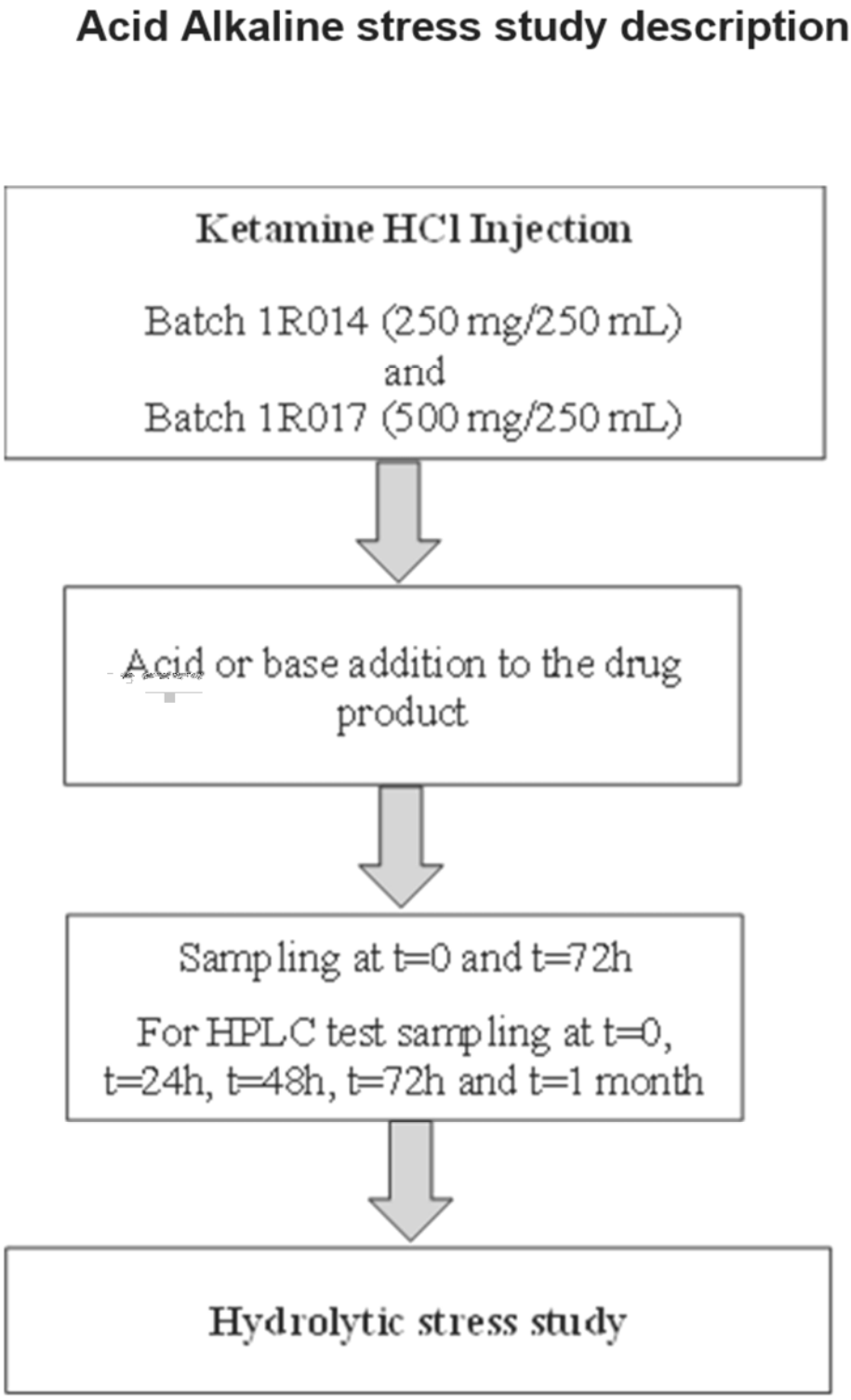

Acid Alkaline stress study description
Ketamine HCl Injection
Batch 1R014 (250 mg/250 mL)
and
Batch 1R017 (500 mg/250 mL)
Acid or base addition to the drug product
Sampling at t=0 and t=72h
For HPLC test sampling at t=0, t=24h, t=48h, t=72h and t=1 month
Hydrolytic stress study

Fig. 2

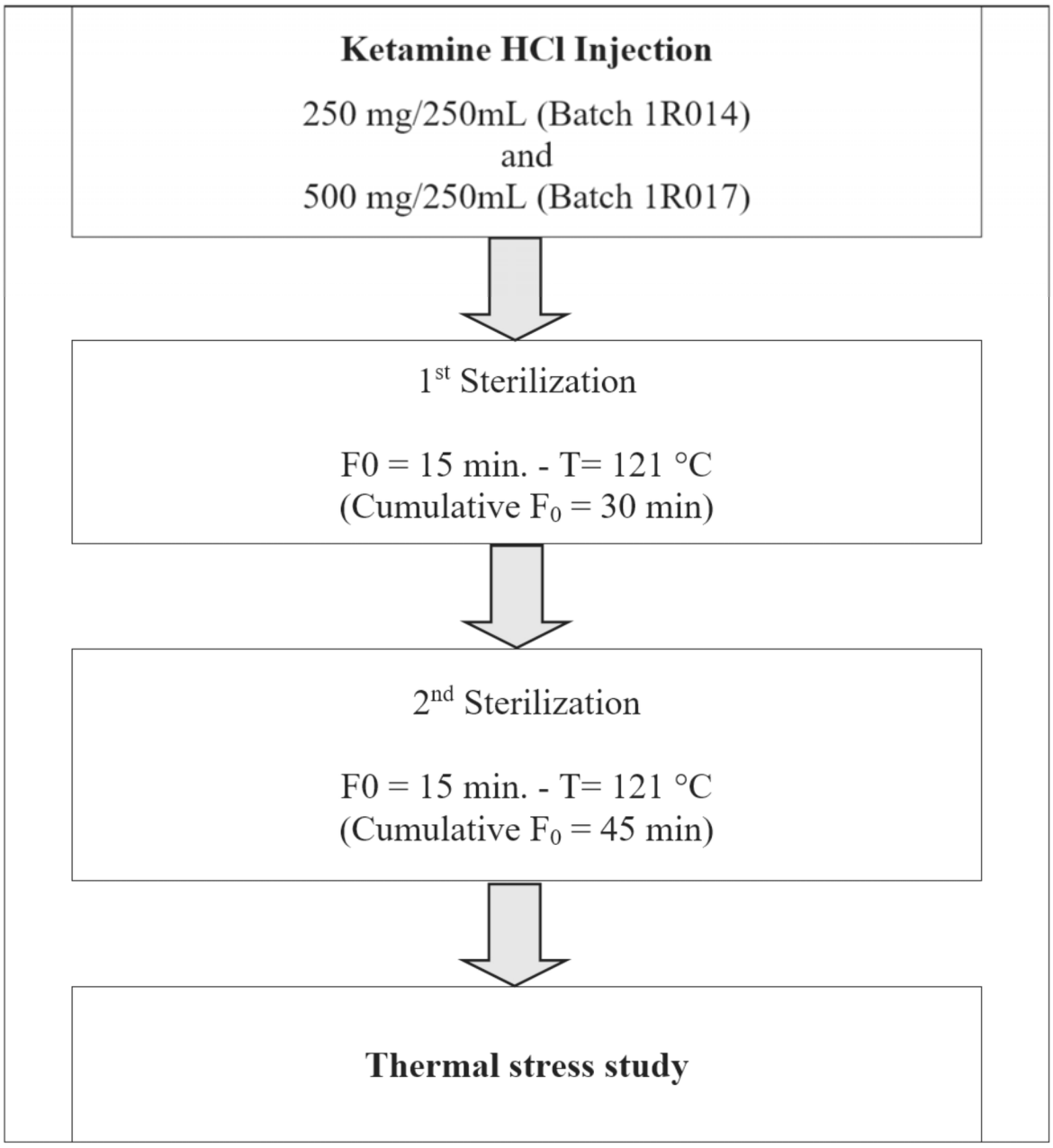

Ketamine HCl Injection
250 mg/250mL (Batch 1R014)
and
500 mg/250mL (Batch 1R017)
1st Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 30 min)
2nd Sterilization
F0 = 15 min. - T= 121 °C
(Cumulative F0 = 45 min)
Thermal stress study

Fig. 3

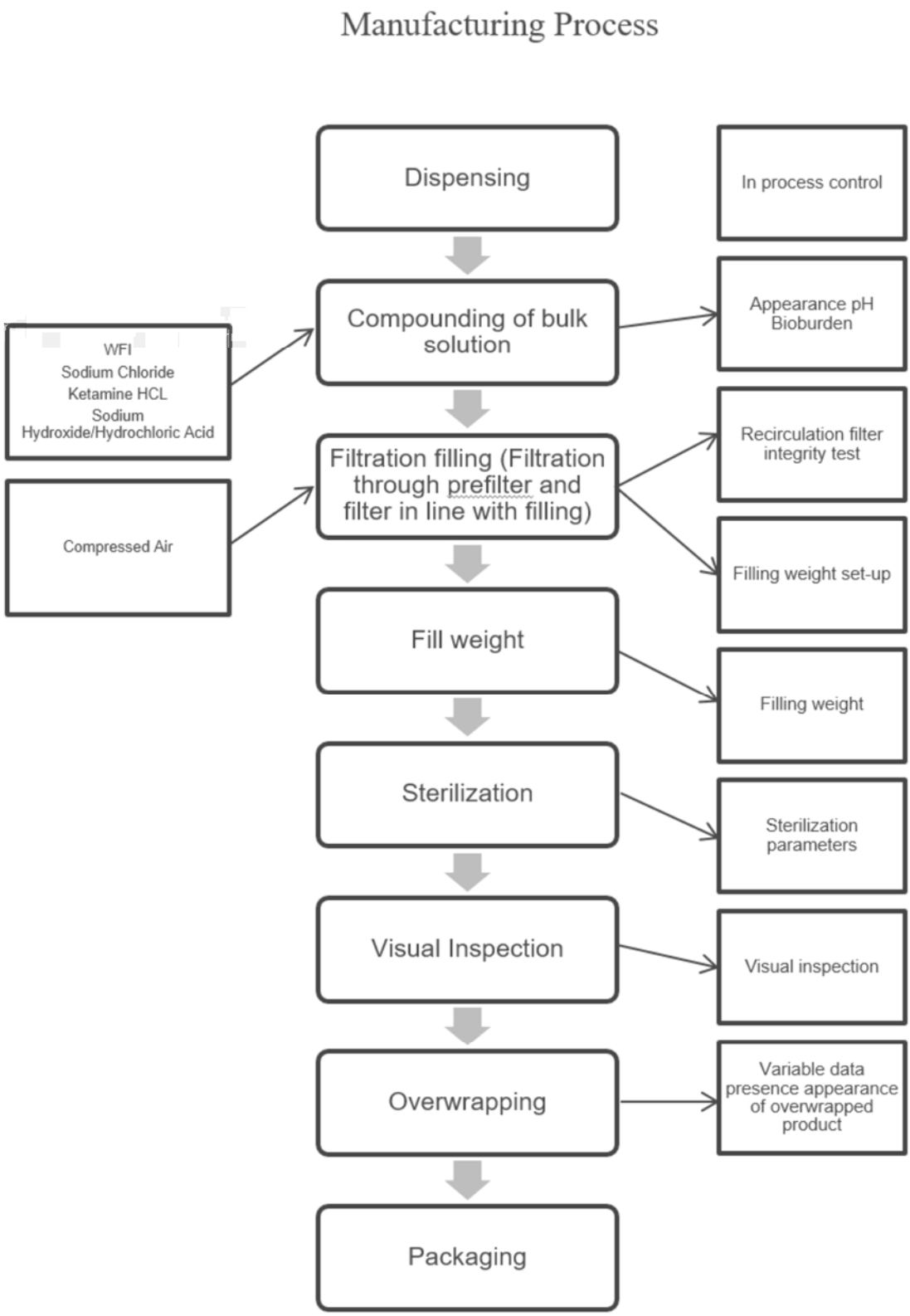

Manufacturing Process
Dispensing
In process control
Compounding of bulk solution
Appearance pH Bioburden
WFI
Sodium Chloride
Ketamine HCL
Sodium Hydroxide/Hydrochloric Acid
Filtration filling (Filtration through prefilter and filter in line with filling)
Recirculation filter integrity test
Filling weight set-up
Compressed Air
Fill weight
Filling weight
Sterilization
Sterilization parameters
Visual Inspection
Visual inspection
Overwrapping
Variable data presence appearance of overwrapped product
Packaging

Fig. 4

Graph 1: Ketamine Injection 1 mg/mL Dissolution Assay

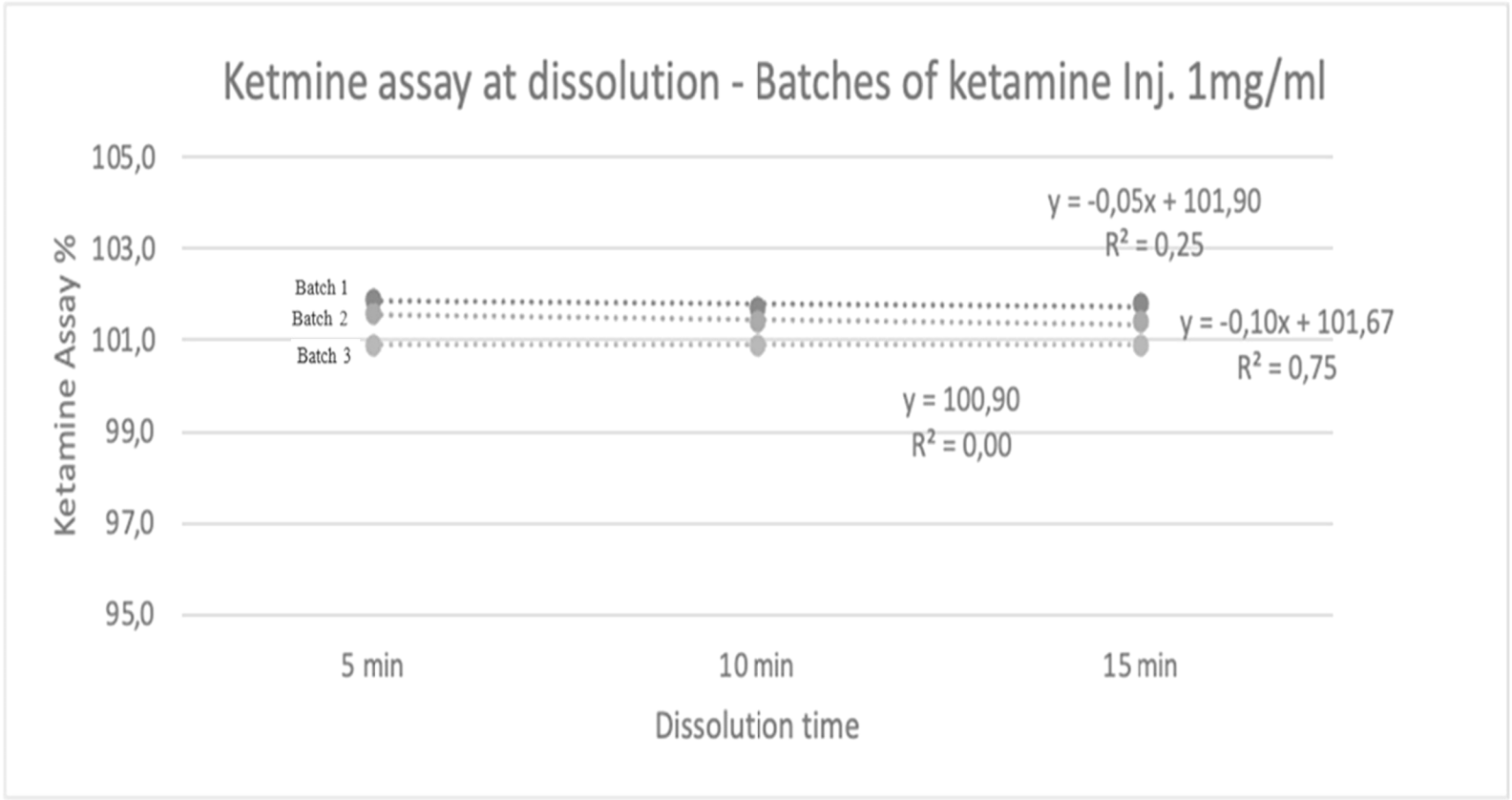


Fig. 5

Graph 2: Ketamine Injection 2 mg/mL Dissolution Assay

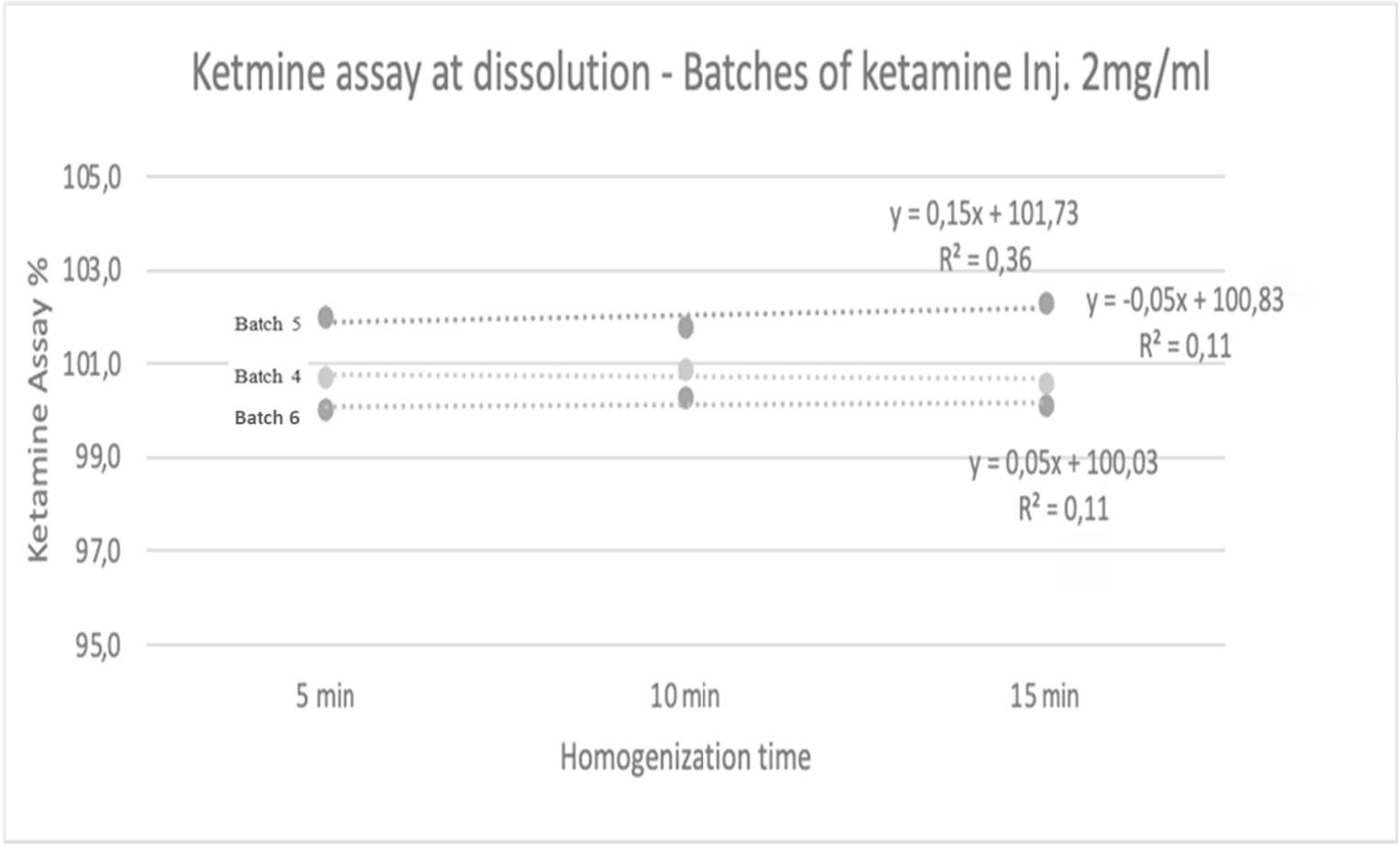


Fig. 6

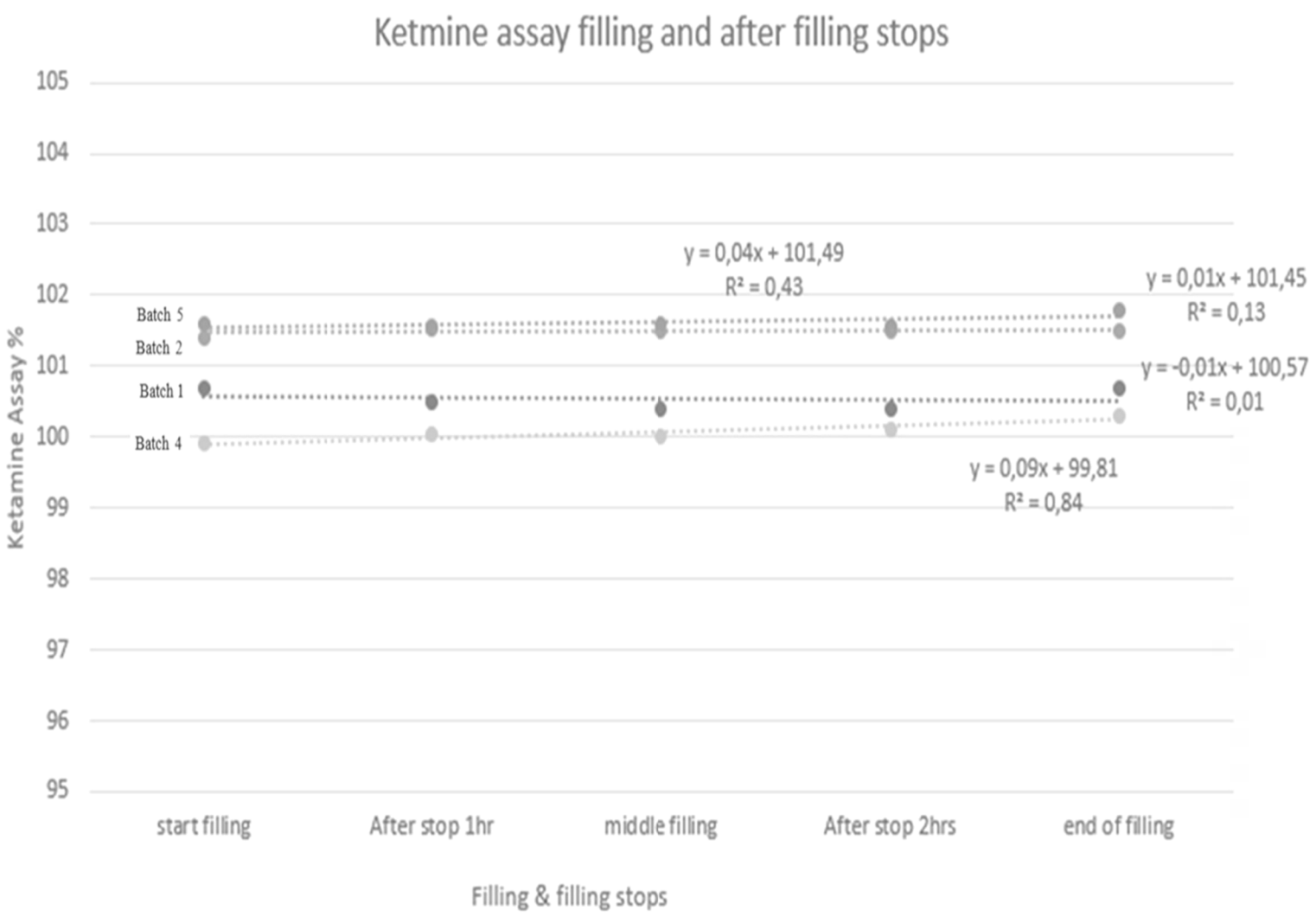

Ketmine assay filling and after filling stops
105
104
103
102
101
100
99
98
97
96
95
Ketamine Assay %
Batch 5
Batch 2
Batch 1
Batch 4
y = 0,04x + 101,49
R² = 0,43
y = 0,01x + 101,45
R² = 0,13
y = -0,01x + 100,57
R² = 0,01
y = 0,09x + 99,81
R² = 0,84
start filling
After stop 1hr
middle filling
After stop 2hrs
end of filling
Filling & filling stops

Fig. 7

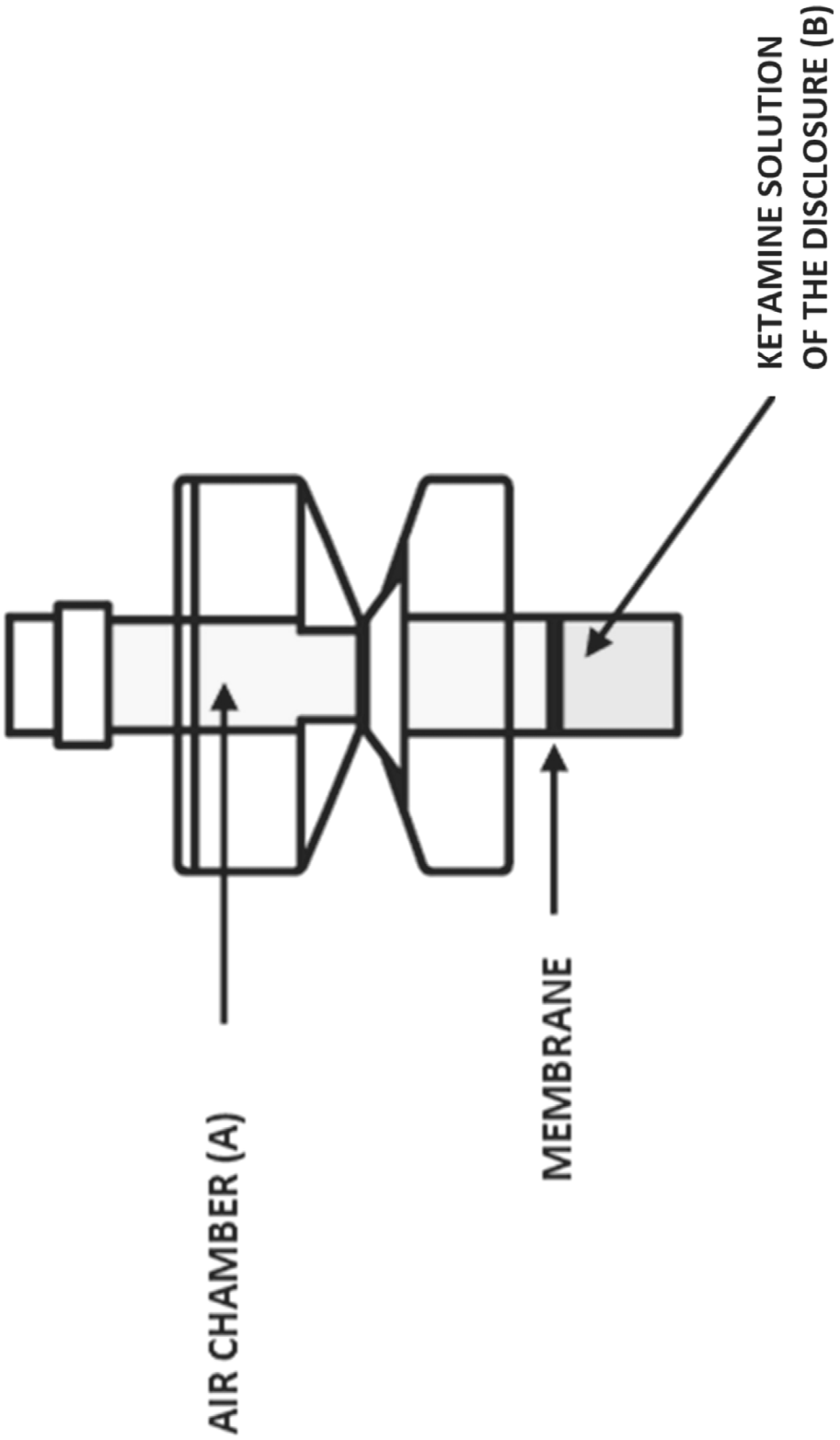


Fig. 8

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READY-TO-USE KETAMINE PREMIX FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority benefit of U.S. provisional application No. 63/513,225, filed Jul. 12, 2023 the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present invention relates to ready-to-use, sterile, premixed formulations of ketamine, or a pharmaceutically acceptable salt thereof, that does not include benzethonium chloride, is chemically stable for approximately 24 months or more, and can be used, for example, to treat a subject in need of anesthesia for a diagnostic or a surgical procedure.

BACKGROUND

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride. Ketamine is a noncompetitive, high affinity NMDA receptor antagonist. Ketamine's mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system. Ketamine has been used as an anesthetic agent.

Most preparations of ketamine contain equal (1:1) concentrations of its two enantiomers: S (+) ketamine and R (−) ketamine. Ketamine formulations that are commercially available and approved by the FDA in the U.S. currently contain benzethonium chloride added as a preservative.

Ketamine can be administered to a patient in a variety of ways. For example, ketamine can be used as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Alternatively, ketamine can be administered for the induction of anesthesia prior to the administration of other general anesthetic agents or as a supplement to other anesthetic agents.

The container closure system of a product intended for parenteral use has to ensure continuous compliance with the storage and handling specifications throughout the product shelf life to maintain functionality and drug delivery accuracy. Several factors have to be considered when choosing the right container closure system for an injectable product, such as drug product formulation properties, dosage, type of application, stability, stability when subjected to extreme conditions (such as during terminal sterilization), sterility, container closure integrity, storage conditions and duration, and end-user friendliness. Thus, there is a need to develop container closure systems that are appropriate for specific injectable products that maintains functionality and drug delivery accuracy.

Vials are the most common primary packaging for administration of ketamine injectables on the market in the U.S. Such vials contain concentrated ketamine solution. For intravenous (IV) administration, it is necessary to introduce the ketamine solution into an infusion container containing a suitably diluted IV solution. Thus, to date, ketamine has been provided as a concentrate that must be diluted with sterile water for injection (WFI), a sodium chloride solution, saline, or a dextrose in water solution prior to administration to a patient and must be used immediately after dilution. If the entire vial is not required, then the vial must still be disposed of as the vials are single use only.

There is no available single intravenous dosage form that provides a sterile, ready-to-use, stable, liquid formulation of ketamine that can be administered without any manipulation to a patient in need thereof, thereby avoiding a compromise with the sterility, an error in dosing accuracy and/or in medicament preparation etc. There is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine which can be administered to a patient in need thereof without deviation or manipulations and while preserving the sterility of the product, and optionally with a provision for administering along with other medicaments for combination or sequential therapy, if needed or desired. There also is a need for a sterile, ready to use infusion container comprising a shelf-stable, liquid formulation of ketamine that does not contain a preservative or antimicrobial such as benzethonium chloride. Preferably the shelf-life of the sterile, ready to use ketamine solution will be 24 months or more at room temperature.

SUMMARY OF THE INVENTION

In the present invention, the inventors have overcome multiple problems of prior art ketamine formulations, such as additional costs and inconvenience; the risk of potential contamination due to inadvertent medical error; long-term storage of a ready to use dosage of a stable, preservative-free ketamine solution. The inventors have developed a sterile, stable liquid formulation of ketamine in an infusion container that is at a ready to use concentration. For plastic materials being considered for use as primary packing materials for the infusion container, the challenge has been to develop packaging that is compatible with the contents, minimizes extractables/leachables, are solvent-resistant, and are durable. The packaging of a pharmaceutical product should desirably be stable and mutually compatible under terminal sterilization conditions, as packaging materials and terminal sterilization can affect the condition of different formulations. A sterile ready to use ketamine formulation in an infusion container avoids the expense, inconvenience, delay, and risk of contamination, and provides significant advantages over currently available concentrated formulations. Additionally, the inventors have beneficially developed a formulation of ketamine that is shelf-stable in an infusion container for greater than three months, and preferably for 24 months or more, without the use of preservatives or antimicrobials such as benzethonium chloride.

The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an intravenous bag or other infusion container. The ready-to-use premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, e.g., in a ready-to-use infusion bag (also referred to as a "ready-to-use bag").

In one aspect, the ketamine product of the disclosure is a ready-to-use, sterile, infusion bag comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection. In one aspect, the ketamine product is terminally sterilized. In one aspect, the ketamine product comprise a sterile aqueous ketamine solution that is aseptically filled, for example, the sterile aqueous ketamine solution is filled under aseptic conditions into a sterile infusion bag. In one

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aspect, the ketamine product of the disclosure is free of a preservative or antimicrobial such as benzethonium chloride.

In one aspect, the ready-to-use, sterile, infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

In one aspect, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution without benzethonium chloride is about 3.5 to 5.5.

In one aspect, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, and a complexing agent. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

In one aspect, the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution is formulated as a total volume of about 50-500 mL.

In one aspect, the ready-to-use, sterile, infusion bag comprising aqueous ketamine solution without benzethonium chloride comprises at least one port. In one aspect, the ready to use terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride comprises at least one tube port closed with a closure. In certain aspects, the closure is a twist off closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the twist off closure comprises a membrane that creates a barrier, splitting the twist-off closure in two parts. In certain aspects, the twist off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure as illustrated in FIG. **8**. In certain aspects, the twist off closure comprises at least one layer of polypropylene. In certain aspects, the closure is a rubber stopper. In certain aspects, the twist off closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises a plastic material. In certain aspects, the closure is a cap. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer. In certain aspects, the tube port comprises one or more layers of a plastic material.

In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible multilayer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, filling, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof etc. In certain aspects, the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a flexible multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a flexible multilayer film in which certain layers are comprised of different polymers or polymer blends from other layers. In one aspect, the infusion bag comprises a flexible film. In certain aspects, the film is a flexible single layer film.

In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a flexible intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use terminally sterilized aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

In one aspect, the infusion container may be enclosed in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized by autoclaving. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using steam sterilization. In one aspect, the ready-to-use infusion container comprising an aqueous ketamine solution without benzethonium chloride is terminally sterilized using heat sterilization. In one aspect, the ready-to-use infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by radiation. In one aspect, the ready-to-use, infusion container comprising a aqueous ketamine solution without benzethonium chloride is terminally sterilized by chemical sterilization (e.g., ethylene oxide).

In one aspect, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than three months at room temperature. In some aspects, the ketamine product in a ready-to-use, sterile container comprising an aqueous ketamine solution without benzethonium chloride has a shelf-life of greater than six months, greater than twelve months, greater than eighteen months, or greater than twenty-four months at room temperature. In one aspect, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15-30° C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25° C.±2° C. with relative humidity (RH) at 40%±5% when stored in the ready-to-use, terminally sterilized, infusion container.

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In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 6000 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 μm present in the aqueous ketamine solution without benzethonium chloride of the disclosure units tested does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 μm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising an aqueous ketamine solution without benzethonium chloride is stored at room temperature for at least 24 months.

In one aspect, the impurities in the ready-to-use, sterile, infusion bag comprising a aqueous ketamine solution without benzethonium chloride total not more than 1%, not more than 0.4%, not more than 0.3%, not more than 0.2%, not more than 0.15%, or not more than 0.05%, or not more than 0.01%.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 98%, greater than 99%, or greater than 99.5%, or greater than 99.9%, or greater than 99.95%.

In one aspect, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In one aspect, the bacterial endotoxin in the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 99% or greater.

In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized, infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (iv); (vii) overwrapping the terminally sterilized infusion bag of step (vi) with an overwrap. In certain aspects, the terminal sterilization is conducted by autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C. for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C. for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C. for about 15 minutes. In certain aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat ensures a hermetic seal between the tube port and the film and the tube port and closure.

In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution from the ready-to-use, sterile infusion bag to the subject without diluting the ketamine solution; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the steps and specifications of the oxidative stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine product of the disclosure"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were spiked with hydrogen peroxide at different ratios (1:1 and 1:10). HPLC tests were performed to determine the effects of oxidative stress on the ketamine HCL injection product.

FIG. **2** shows the steps and specifications of the acid alkaline stress study conducted on the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). An acid or base was added to two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively). HPLC tests were performed to determine the effects of hydrolytic stress on the ketamine HCL injection product.

FIG. **3** shows the steps and specifications of the thermal stress study conducted on the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure ("ketamine HCL injection"). Two batches of ketamine HCL injection (1R014 and 1R017) at two different concentrations (1 mg/mL and 2 mg/mL respectively) were subjected to two autoclave cycles. Tests were performed to determine the effects of thermal stress on the ketamine HCL injection product, the results of which are shown in tables 22 and 23.

FIG. **4** shows the manufacturing steps for the ready to use terminally sterilized infusion bag comprising a preservative-free aqueous ketamine solution of the disclosure.

FIG. **5** shows the results of process sampling and analysis of bulk solution for three batches of the ketamine solution of the disclosure at 1 mg/mL.

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FIG. **6** shows the results of process sampling and analysis of bulk solution for 3 batches of the ketamine solution of the disclosure at 2 mg/mL.

FIG. **7** shows the results of a filter compatibility and filling study for 4 batches of the ready to use sterile infusion bag comprising a preservative-free aqueous ketamine solution at two different concentrations. Batches 1 and 2 are at 1 mg/mL of ketamine and batches 4 and 5 are at 2 mg/mL of ketamine.

FIG. **8** shows a diagram of a twist off closure that may be used with a sterile infusion bag comprising an aqueous ketamine solution of the disclosure.

DETAILED DESCRIPTION

The present invention includes ketamine prepared in a premixed, ready to use, formulation that does not require reconstitution or dilution prior to administration to a patient. In one aspect, the ketamine product of the disclosure is terminally sterilized in an infusion container with high integrity, and remains stable and active after prolonged storage. In another aspect, the ketamine product of the disclosure is produced under aseptic conditions. Such premixed formulations therefore avoid the cost, inconvenience, and risk of contamination or overdose that can be associated with reconstituting or diluting a concentrated ketamine formulation prior to administration to a patient. The present invention includes ready-to-use ketamine formulations that do not comprise a preservative, or that do not contain an antimicrobial such as benzethonium chloride, but remain sterile and stable when stored at room temperature for a prolonged period (e.g., 24 months) in a sterile infusion container.

The present invention relates to premixed pharmaceutical compositions of ketamine, or a pharmaceutically acceptable salt thereof, in an infusion container. The premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration, and remain active after prolonged storage.

In one aspect, the present invention of the disclosure is a ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection.

In certain aspects, the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride comprises ketamine at a concentration of about 1 to about 2 mg/mL. In certain aspects, the pharmaceutically acceptable salt is ketamine hydrochloride. In certain aspects, the tonicity adjustment agent comprises sodium chloride.

In certain aspects, the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof. In certain aspects, the pH of the aqueous ketamine solution is about 3 to 6. In certain aspects, the pH of the aqueous ketamine solution is about 3.5 to 5.5.

In certain aspects, the liquid pharmaceutical composition is free of a preservative. In certain aspects, the preservative-free aqueous ketamine solution is free of a chelating agent, an antioxidant, a stabilizer, a complexing agent and a preservative. In certain aspects, the aqueous ketamine solution is antimicrobial-free (e.g., free of benzethonium chloride), but may contain one or more chelating agents, complexing agents, stabilizers, and/or antioxidants.

In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg. In certain aspects, the aqueous ketamine solution without benzethonium chloride is formulated as a total volume of about 50-500 mL.

In one aspect, the primary packaging for the ready-to-use, sterile aqueous ketamine solution without benzethonium chloride is an intravenous bag. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a pre-filled syringe. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a glass container. In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is a plastic bottle or semi-flexible IV container.

In one aspect, the intravenous bag is made up of multilayer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer. Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

In one aspect, the primary packaging for the ready-to-use, sterile, aqueous ketamine solution without benzethonium chloride is an infusion container. In certain aspects, the infusion container is a flexible infusion bag. In certain aspects, the infusion bag comprises at least one port. In certain aspects, the infusion container is a prefilled syringe. In certain aspects, the infusion container is a glass container. In certain aspects, the infusion container is a semi-flexible plastic infusion container.

In one aspect, the ready to use, sterile infusion bag, comprising an aqueous ketamine solution without benzethonium chloride comprises at least one port. In some aspects, the port is a tube port closed with a closure. In certain aspects, the tube port comprises a multilayer polyolefin and styrene block copolymer tube material. In certain aspects, the tube port comprises at least one layer of block copolymer. In certain aspects, the tube port comprises multiple layers of a block copolymer. In certain aspects, the tube port comprises multiple layers of a polyolefin block copolymer at least one port is a tube port. In certain aspects, the tube port comprises one or more layers of a plastic material.

In some aspects, the tube port comprises a PP/EVA material. In some aspects, the tube port comprises a multilayer co-extruded connector tubing. In some aspects, the tube port is PVC-free and/or plasticizer free. In some aspects, the tubing port is sealed closed. Other polymers that

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are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the port.

In certain aspects the closure is a twist-off closure. In certain aspects, the closure comprises a membrane that creates a barrier, splitting the closure in two parts. In certain aspects, the closure comprises an inferior part of the membrane in direct contact with the ketamine solution, while the superior part is in contact with a zone that forms an air chamber into the closure. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, the closure comprises at least one layer of polyethylene. In certain aspects, the closure comprises at least one layer of polypropylene. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the closure.

In certain aspects, the port may have a stopper, such as a rubber stopper, to provide a fluid tight closure of the passage and a lid member that clamps the periphery of the stopper. In certain aspects, the port may have a stopper comprising a plastic material. In a non-limiting embodiment, the port may have a resalable stopper which provides fluid tight closure of the passage and a plastic cap that clamps the periphery of the resealable stopper. Other closure systems that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In a non-limiting embodiment, the port may be a resealable twist off port, which may also be referred to as a "spike port." In some embodiments, the infusion container of the present invention may optionally be overwrapped by an overwrap pouch covering the filled and sealed infusion container. In some embodiments, the infusion container is overwrapped by an aluminum pouch, which may further comprise other materials or a combination of other materials, for example, a four layer overwrap. The present invention does not relate to semi-solid topical formulations (such as gel, hydrogel, emulgel, paste, cream, ointment etc.), inhalations or aerosols and/or non-aqueous formulations that are not suitable for parenteral administration.

In one aspect, the infusion bag comprises a flexible film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials such as polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof, etc. In certain aspects, the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation; an M315 film manufactured by SealedAir Corporation; an APP-series film manufactured by Polycine, such as APP-114S film manufactured by Polycine; a polypropylene film, such as those manufactured by Technoflex, such as an Inerta® film manufactured by Technoflex; a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa; an Inerta 103 film, made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer, which may be manufactured by Technoflex; or another commercially-available polymer film designed for use in intravenous bag products. In certain aspects, other polymers that are stable, with low leachables, and without physical deformation during terminal sterilization may also be used for the infusion bag.

In certain aspects, the infusion container (e.g., infusion bag) is contained in an overwrap. In certain aspects, the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof. In certain aspects, the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

Aseptic processing involves sterile filtration and aseptic processing of a pharmaceutical product, wherein a premixed pharmaceutical solution is sterilized, for example, by filtering a pharmaceutical solution through a pre-filter with a filter absolute rating: 0.45 μm followed by a filtration through two sterilizing filters (0.2 μm pore size filters) under aseptic conditions, or similar conditions. The filtration can be pressure driven (conducted under compressed air). Aseptic filling of the sterile solution into a sterile container can be achieved, for example, by filling the pre-sterilized bag in line with filtration under aseptic conditions. After filling, port of the infusion bags used for product solution filling can be sealed.

Terminal sterilization involves sterilizing a pharmaceutical product in its sealed final container (e.g., in an infusion bag). A sterilizing agent or process is used to kill microbes and other pathogens to create a sterile final product. Terminal sterilization of ketamine formulations in infusion bags can be achieved by steam sterilization, heat sterilization, such as an autoclave method or any other methods known in the art; by radiation treatment such as Gamma, E-beam or ultraviolet; or by chemical sterilization, e.g., ethylene oxide. See, e.g., U.S. Pat. Nos. 5,439,643 and 8,617,467, each incorporated herein by reference in their entireties. Heat sterilization may include steam sterilization and autoclaving. A terminally sterilized drug product undergoes final sterilization in a sealed container, and thus, enhances safety by reducing the risk of contamination. Terminal sterilization is one of the most difficult requirements for medical devices. It eliminates viable pathogens (e.g., microbes and viruses) to produce a sterile final product, but it involves conditions that can affect the integrity of the packaging, cause leaching of packaging components into the pharmaceutical solution, cause degradation of the drug product, and/or otherwise affect the stability the pharmaceutical solution. Every component of an infusion bag that is subjected to terminal sterilization (including the bag film, ports, and closures) must be able to withstand terminal sterilization conditions and must be compatible with the pharmaceutical solution components under those conditions.

In certain aspects, the terminal sterilization procedure of the ready to use terminally sterilized infusion container

comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is autoclaving. Autoclaving involves application of elevated temperature and/or pressure to achieve sterilization. Other methods of terminal sterilization (e.g., ethylene oxide, radiation) also involve harsh conditions. Subjecting a pharmaceutical composition in a final container to terminal sterilization can adversely affect the pharmaceutical composition, the material of the final container, and the sealing integrity of the final container. Thus, not all pharmaceutical compositions and final containers are mutually suitable for terminal sterilization using heat sterilization. Heat sterilization may be performed using steam, preferably wet steam, or superheated water. The time period for the sterilization must be long enough to meet the sterility requirements required of an injectable product. When steam is used the period may be from about 5 to 30 minutes at temperatures of about 110° C. to 130° C., or from about 10 to 30 minutes at temperatures of about 110° C. to 130° C., preferably at 120° C. to 125° C. for 15 to 30 minutes. In another aspect, the sterilization can be at 120° C. for 15 to 20 minutes. The pharmaceutical formulation should be analyzed after sterilization for the presence of leachables and other impurities.

In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof in a ready-to-use, sterile infusion container comprising a preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure is chemically stable for at least 24 months when stored at a controlled room temperature. In certain aspects, the controlled room temperature is 15-30° C. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25° C.±2° C. with relative humidity (RH) at 40%±5% when stored in the ready-to-use, terminally sterilized, infusion container. In certain aspects, the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25° C.±2° C. with relative humidity (RH) at 40%±5% when stored in the ready-to-use, sterile, infusion container.

In certain aspects, the average number of particles equal to or greater than 10 μm present in the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure units tested does not exceed 6000 per container when the sterile infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In one aspect, the average number of particles equal to or greater than 10 μm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 600 per container. In one aspect, the average number of particles equal to or greater than 10 μm present in the preservative-free or antimicrobial-free aqueous ketamine solution does not exceed 60 per container. In certain aspects, the average number of particles equal to or greater than 25 μm present in the units tested does not exceed 600 per container when the terminally sterilized infusion bag comprising a preservative-free or antimicrobial-free aqueous ketamine solution is at room temperature for at least 24 months. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 23, e.g., 0 to 23, 0 to 15, 0 to 10, 0 to 5, 0 to 4, 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 10 microns in size. In certain aspects, the preservative-free or antimicrobial-free aqueous ketamine solution of the disclosure comprises contains not more than 3, e.g., 0 to 3, 0 to 2, 0 to 1, or 0 particulates greater than or equal to 25 microns in size.

In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are less than or equal to 1%. In certain aspects, the impurities in the ready-to-use, sterile infusion container comprising an aqueous ketamine solution without benzethonium chloride are not more than 2%, not more than 1.5%, not more than 1%, not more than 0.5%, not more than 0.2%, not more than 0.15%, or not more than 0.05%.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 99.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 99%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 98.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 98%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 97.5%. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 97%.

In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is about 0.4 EU/mg. In certain aspects, the bacterial endotoxin in the aqueous ketamine solution without benzethonium chloride of the disclosure is less than about 0.4 EU/mg, for example, less than about 0.3 EU/mg, less than about 0.2 EU/mg, or less than about 0.1 EU/mg.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine without benzethonium chloride solution of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99.9% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution of the disclosure after long-term storage for months at 25° C.±2° C./40% RH±5% RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 97% or greater.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25°

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C.±2° C./40% RH±5% RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 18 months at 25° C.±2° C./40% RH±5% RH is 97% or greater.

In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 99% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 98.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 98% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 97.5% or greater. In one aspect, the ketamine content of the sterile, aqueous ketamine solution without benzethonium chloride of the disclosure after long-term storage for 24 months at 25° C.±2° C./40% RH±5% RH is 97% or greater.

In one aspect, the present invention includes a method of preparing the ready-to-use, terminally sterilized infusion bag comprising a aqueous ketamine solution without benzethonium chloride of the disclosure, comprising: (i) adding ketamine or a pharmaceutically acceptable salt thereof to water; (ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent; (iii) filtering the solution of step (ii); (iv) filling the solution into an infusion bag, for example, through the tube port; (v) terminally sterilizing the infusion bag of step (v); (vi) overwrapping the terminally sterilized infusion bag of step (v) with an overwrap. In certain aspects, the terminal sterilization is autoclaving. In certain aspects, said autoclaving is at a temperature ranging from 110 to 130° C. for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C. for a period of time ranging from 7 to 60 minutes. In certain aspects, said autoclaving is at a temperature of 121° C. for about 15 minutes. In certain aspects, no glue is used to seal the tube port to the film or the closure to the tube port; autoclave heat insures a hermetic seal between the tube port and the film and tube port and closure.

In one aspect, the present invention includes a method of treating a subject in need of analgesia, comprising administering the ketamine solution using the ready-to-use, sterile infusion bag to the subject; and wherein the ketamine is administered as a continuous infusion. In certain aspects, the ketamine solution is administered by an intravenous infusion.

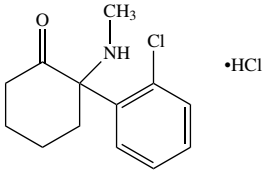
In one aspect, the subject is in need of anesthesia for a diagnostic or a surgical procedure. In certain aspects, the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

In one aspect, the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.

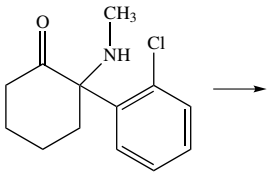
Definitions

The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the present disclosure and how to make and use them.

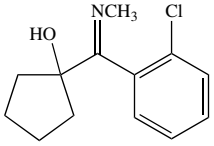
As used herein, the term "ketamine" refers to (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone as the free base or in the form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of ketamine can include inorganic acid salts such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. In certain aspects, the ketamine salt is ketamine HCl. In other non-limiting embodiments, ketamine comprises the structure depicted below in Formula I:



Ketamine in aqueous solution has been shown to react under accelerated conditions of high temperature and pH by a process which involves initial formation of 1-[(2-chlorophenyl) (15ethylamino) methyl] cyclopentanol ("Compound A"). Thus, the term "Compound A" or "Impurity A" as used herein comprises the structure on the right-hand side of the reaction depicted below:

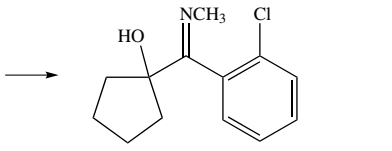


Ketamine

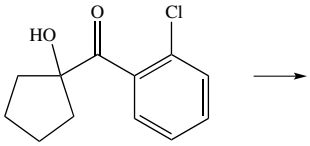


1-[(2-chlorophenyl)(methylimino)methyl] cyclopetanol (Ph. Eur. impurity A, USP related compound A)

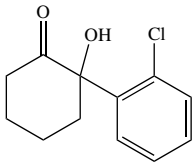
Compound A, depending on temperature and pH, may then isomerize back to Ketamine or hydrolyze to the primary product of this reaction: (2-chlorophenyl)(1-hydroxycyclopentyl) methanone 2-(2-chlorophenyl)-2-hydroxycyclohexanone ("Impurity B") which may be major, although not primary product, that results from isomerization of (2-chlorophenyl)(1-hydroxycyclopentyl)methanone ("Impurity C"). The structures of "Compound A" (also referred to as "Impurity A"), "Impurity B," and "Impurity C," are depicted in the reaction below:



1-[(2-chlorophenyl)(methylimino)methyl] cyclopetanol (Ph. Eur. impurity A, USP related compound A)



(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (Ph. Eur. impurity C)



2-(2-chlorophenyl)-2-hydroxy cyclohexanone (Ph. Eur. impurity B)

The term, "chemically stable," as used herein, refers to a chemical compound which retains its chemical structure and useful properties on a timescale of its expected usefulness. Specifically, the usefulness of the compound is maintained in the environment in which it is stored. Conversely, a compound lacks chemical stability if it decomposes under the conditions of a specific environment. As used herein in certain embodiments, "chemically stable" may mean resistant to degradation of ketamine into its known or unknown decomposition elements. The level of ketamine identified impurity that is acceptable can be up to 0.15% of the formulation as per the ICH guidelines for shelf-life determination, but in certain preferred embodiments, the amount of impurities is lower, e.g., less than 0.05% of the formulation.

As used herein, the terms "premix", "premixed", or "premixture" refers to a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of ketamine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.

As used herein, the term "ready-to-use" or "ready to use" refers to premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).

As used herein, the term "container closure system" refer to the sum of packaging components that together contain and protect the dosage form, including primary packaging components and secondary packaging components.

As used herein, the terms "primary packaging components," "primary packaging" means packaging components that are or may be in direct contact with the dosage form. For example, the primary packaging may be an infusion bag, including a flexible film component, one or more ports, and a closure system.

The terms "infusion bag," "intravenous bag," and "IV bag" may be used interchangeably herein and refer to a type of primary packaging, which comprises a bag film, port(s) and closure system(s). Such infusion bags may be used to administer intravenous infusion products.

The term "infusion container" as used herein refers to a type of primary packaging used to administer intravenous infusion products, for example, a flexible infusion bag, a semi-flexible plastic infusion container, a prefilled syringe, etc.

As used herein, the term "flexible" refers to a material that has the ability to deform and return to its original shape when the applied stress is removed without breaking or damage at around standard temperature and pressure (STP), for example about 0° C.±40° C. and 1 atm±0.005 atm. Flexible materials are distinguished from rigid materials such as glass. A "flexible" infusion bag allows fluid to drain out of the bag without venting. A "flexible" infusion bag may have port tubes and/or closures that are made of rigid or semi-rigid materials, provided that the bag film is flexible.

As used herein, the terms "secondary packaging components" and "overwrap" refer to a packaging component that is intended to provide additional protection to the drug product but is not typically in direct contact with the dosage form during storage.

As used herein, the terms "subject" or "patient" refer to a human, a non-human mammal or a non-human animal. The compounds and compositions of the present disclosure have application in veterinary medicine as well as for humans, e.g., for the treatment of domesticated species such as canine, feline, and various other pets; farm animal species such as bovine, equine, ovine, caprine, porcine, etc.; wild animals, e.g., in the wild or in a zoological garden; and avian species, such as chickens, turkeys, quail, songbirds, etc.

As used herein, the terms "pharmaceutical composition" or "pharmaceutical formulation" relates to compositions that can be formulated in any conventional manner using one or more pharmaceutically acceptable diluents or excipients. A "pharmaceutically acceptable" solvent, diluent or excipient, as used herein, means approved by a regulatory agency of the federal or a state government, or as listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans. Suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions).

As used herein, the terms "therapeutically effective dose," "dose," "effective amount," and "therapeutically effective amount" refer to an amount sufficient to produce the desired effect, which can be readily determined according to standard good medical practice by those of skill in the art. In

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other non-limiting embodiments, a therapeutically effective dose or effective amount may be any amount that produces a response that a user (e.g., a clinician) will recognize as an effective response to the therapy. Thus, a therapeutically effective amount will generally be an amount that induces a desired effect, such as, for example, sedation or analgesia.

As used herein, the terms "about" and "approximately" mean+/–20% of the recited value, or within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system.

As used herein, the terms "intensive care unit" or "ICU" refer to any setting that provides intensive care.

As used herein, the terms "port," "tubing port," or "port tube" refer to a connector which is sealed into the container portion of an infusion bag. An infusion bag may include one or more ports. The ports may include administrative and/or additive ports. The ports of the invention use commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization. The ports may be coextruded.

As used herein, the term "closure" refers to a component that closes or seals a container. A closure provides an effective barrier against microbial contamination. In some aspects, the closure is a twist off closure. The closures referred to herein may comprise commerciality available polymers, elastomers, etc. and can comprise one or more layers, which can withstand terminal sterilization.

As used herein, singular forms, including the singular forms "a" "an" and "the", specifically also encompass the plural referents of the terms to which they refer unless the context clearly dictates otherwise. In addition, as used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

Pharmaceutical Formulations

The compounds and compositions of the invention may be formulated as pharmaceutical compositions by admixture with pharmaceutically acceptable solvents and excipients. For example, suitable components of pharmaceutical compositions are described in, for example, "Remington's Pharmaceutical Sciences" by Philip P. Gerbino, 21st Edition (or previous editions). In certain non-limiting embodiments, the compounds or compositions are provided in a therapeutically effective amount to an animal, such as a mammal, preferably a human, in need of treatment therewith for inducing a sedative, anxiolytic, analgesic, or anesthetic effect.

In certain non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is the only therapeutically active ingredient present in the composition. In another non-limiting embodiments, ketamine is formulated as a pharmaceutical composition, wherein the ketamine is formulated in combination with at least one or more other therapeutically active ingredient. The formulation is suitable for parenteral administration, such as intravenous administration.

The pharmaceutical formulations suitable for injectable use, such as, for example, intravenous administration, include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. Solvents or dispersion mediums suitable for stable pharmaceutical formulations include, for example, water for injection (WFI), saline, aqueous dextrose, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and oils. In certain aspects, the solvent may be sterile WFI, 0.9% sodium chloride injection (normal saline), or 5% dextrose in water. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like. Exposure to potential microorganisms such as bacteria, viruses, and fungi can also be prevented using terminal sterilization of prefilled parenteral pharmaceutical products and packages or aseptic processing throughout the manufacturing process of the ketamine product.

Pharmaceutical formulations may include isotonicity adjusting agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions may be prepared by incorporating the ketamine in the required amounts in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtering and/or terminal sterilization.

Pharmaceutical formulations may include one or more excipients. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer; amino acids; urea; alcohols; ascorbic acid; phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrrolidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine; lipids; preservatives; suspending agents; stabilizers; and dyes. The term "stabilizer" refers to a compound optionally used in the pharmaceutical compositions of the present invention in order to increase storage life. Non-limiting examples of stabilizers include antioxidants. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers.

Pharmaceutical formulations may include a non-ionic surfactant. Preferred non-ionic surfactants include Polysorbate 20, Polysorbate 80, Triton X-100, Triton X-114, Nonidet P-40, Octyl α-glucoside, Octyl β-glucoside, Brij 35, Pluronic, and Tween 20.

Methods of Using Ready to Use Ketamine Compositions

As noted above, the methods of treatment of the invention are directed to methods of analgesia in a patient in need thereof comprising administration of ketamine to the patient, wherein the ketamine is administered in an amount effective to produce the desired effect.

The ketamine for use in the invention can be administered via any suitable route. In a non-limiting embodiment, the therapeutic compound can be delivered in a controlled or

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sustained release system. For example, a compound or composition may be administered using intravenous infusion, continuous infusion, or other modes of administration. In certain non-limiting embodiments, the dosage of ketamine can be individualized and titrated to the desired clinical effect.

The present disclosure includes the following non-limiting list of items:

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is free of benzethonium chloride, and wherein the ketamine product is sterile and ready-to-use (RTU).
2. The ketamine product of item 1, wherein the ketamine product has been terminally sterilized.
3. The ketamine product of any preceding item, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.
4. The ketamine product of any preceding item, wherein the aqueous ketamine solution is preservative-free or antimicrobial-free.
5. The ketamine product of any preceding item, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerine, mannitol, potassium chloride, or any combination thereof.
6. The ketamine product of any preceding item, wherein the aqueous ketamine solution comprises 0.9% sodium chloride.
7. The ketamine product of any preceding item, further comprising a pH adjusting agent.
8. The ketamine product of item 7 wherein the pH adjusting agent comprises hydrochloric acid, sodium hydroxide, or a combination thereof.
9. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3 to 6.
10. The ketamine product of any preceding item, wherein the pH of the aqueous ketamine solution is about 3.5 to 5.5.
11. The ketamine product of any preceding item, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.
12. The ketamine product of any preceding item, wherein the solution comprises one or more of a chelating agent, an antioxidant, a stabilizer, or a complexing agent.
13. The ketamine product of any preceding item, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.
14. The ketamine product of any preceding item, wherein aqueous ketamine solution is formulated as a total volume of about 50-500 mL.
15. The ketamine product of any one of items 11-14, wherein the at least one port comprises a plastic material.
16. The ketamine product of item 15, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.
17. The ketamine product of any one of items 11-16, wherein the closure comprises a plastic material.
18. The ketamine product of any one of items 11-17, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts.
19. The ketamine product of item 18, wherein the twist-off closure comprises an inferior part of the membrane in direct contact with the ketamine solution, and a superior part of the membrane in contact with a zone that forms an air chamber into the closure.
20. The ketamine product of any one of items 18 to 19, wherein the twist-off closure comprises at least one layer of polypropylene.
21. The ketamine product of any one of items 18 to 20, wherein the twist-off closure comprises at least one layer of polyethylene.
22. The ketamine product of any one of items 11-21, wherein the port comprises at least one layer of block copolymer.
23. The ketamine product of any one of items 11-22, wherein the port comprises more than one layer of a block copolymer.
24. The ketamine product of any one of items 11-23, wherein the port comprises more than one layer of a polyolefin block copolymer.
25. The ketamine product of any one of items 11-24, wherein the infusion bag comprises a flexible multilayer film.
26. The ketamine product of any one of items 11-25, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin, polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, or any combination thereof.
27. The ketamine product of any one of items 11-26, wherein the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer.
28. The ketamine product of any one of items 11-27, wherein the infusion bag comprises a flexible multilayer film comprising polypropylene styrene-block copolymer.
29. The ketamine product of any one of items 11-28, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.
30. The ketamine product of any one of items 11-29, wherein the infusion bag comprises a 3-layer film comprising polypropylene styrene-block copolymer.
31. The ketamine product of any one of items 11-30, wherein the infusion bag is contained within an overwrap.
32. The ketamine product of item 31, wherein the overwrap comprises polyester, aluminum, polypropylene, or a combination thereof.
33. The ketamine product of any one of items 31 to 32, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.
34. The ketamine product of any preceding item, wherein the ketamine product has been autoclaved.
35. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is preservative-free, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container.
36. The ketamine product of item 35, wherein the ketamine is at a concentration of about 1 to about 2 mg/mL.
37. The ketamine product of any preceding item, wherein the ketamine product has a shelf-life of more than three months when stored at a controlled room temperature.

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38. The ketamine product of item 37, wherein the controlled room temperature is 15-30° C.
39. The ketamine product of any preceding item, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable for at least 24 months at 25° C.±2° C. with relative humidity (RH) at 40%±5%.
40. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 10 μm does not exceed 600 per container ketamine following storage of the ketamine product at room temperature for 24 months.
41. The ketamine product of any preceding item, wherein the average number of particles equal to or greater than 25 μm does not exceed 60 per container following storage of the ketamine product at room temperature for 24 months.
42. The ketamine product of any preceding item, wherein the total impurities in the aqueous ketamine solution is less than or equal to 1%.
43. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 99%.
44. The ketamine product of any preceding item, wherein the bacterial endotoxin content is less than 0.4 EU/mg.
45. The ketamine product of any preceding item, wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 99% or greater compared to the ketamine content before storage.
46. The ketamine product of any preceding item, containing about 250 mg ketamine hydrochloride.
47. The ketamine product of any preceding item, containing about 500 mg ketamine hydrochloride.
48. A method of preparing the ketamine product of any preceding item, comprising:
    i) adding ketamine or a pharmaceutically acceptable salt thereof to water;
    ii) adjusting the pH to about 3.5 to 5.5 using a pH adjusting agent;
    iii) filtering the solution of step (ii);
    iv) filling the solution of step (iii) into an infusion bag; and
    v) terminally sterilizing the infusion bag of step (iv).
49. The method of item 48 further comprising overwrapping the terminally sterilized infusion bag with an overwrap.
50. The method of any one of items 48-49, wherein the terminal sterilization comprises autoclaving the infusion bag.
51. The method of item 50, wherein said autoclaving is at a temperature ranging from 110 to 130° C. for a period of time ranging from 7 to 60 minutes.
52. The method of any one of items 50-51, wherein said autoclaving is at a temperature of 121° C. for a period of time ranging from 7 to 60 minutes.
53. The method of any one of items 50-52, wherein said autoclaving is at a temperature of 121° C. for about 15 minutes.
54. The method of any one of items 50-53, wherein the method comprises overwrapping the infusion bag of step (iv) prior to terminally sterilizing the infusion bag.
55. A method of treating a subject in need of analgesia, comprising administering the ketamine product of any one of items 1-47 to the subject as a continuous infusion.
56. The method of item 55, wherein the ketamine solution is administered by intravenous infusion.
57. The method of item 55 or item 56, wherein the subject is in need of anesthesia for a diagnostic or a surgical procedure.
58. The method of item 55 or item 56, wherein the subject is in need of anesthesia prior to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.
59. The method of item 55 or item 56, wherein the subject is in need of ketamine administration in addition to administration of an anesthetic agent other than ketamine or a pharmaceutically acceptable salt thereof.
60. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, a pH adjusting agent, and water for injection, wherein the ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is ready-to-use (RTU).

EXAMPLES

The following examples are merely illustrative of the presently disclosed subject matter and they should not be considered as limiting the scope of the present disclosure in any way.

Example 1: Exemplary Formulations

In one embodiment, the ketamine product comprises the composition of Table 1.

TABLE 1

Ketamine Hydrochloride in Sodium Chloride Injection 1 mg/mL

Active Substance(s)	Quantity per Unit (mg/mL)	Quantity per Unit (250 mL container)	Function	Reference Standard
Ketamine as Ketamine HCl	1 mg/mL 1.15 mg/mL	250 mg	API	USP
		Excipient(s)		
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

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In another embodiment, the ketamine product may comprise the composition of Table 2.

TABLE 2

Ketamine Hydrochloride in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	Quantity per Unit (mg/mL)	Quantity per Unit (250 mL container)	Function	Reference Standard
Ketamine as Ketamine HCl	2 mg/mL 2.3 mg/mL	500 mg	API	USP
		Excipient(s)		
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

In another embodiment, the ketamine product may comprise the composition of Table 3.

TABLE 3

Ketamine in Sodium Chloride Injection 1 mg/mL				
Active Substance(s)	Quantity per Unit (mg/mL)	Quantity per Unit (250 mL container)	Function	Reference Standard
Ketamine (free base)	1 mg/mL	250 mg	API	USP
		Excipient(s)		
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

In another embodiment, the ketamine product may comprise the composition of Table 4.

TABLE 4

Ketamine in Sodium Chloride Injection 2 mg/mL				
Active Substance(s)	Quantity per Unit (mg/mL)	Quantity per Unit (250 mL container)	Function	Reference Standard
Ketamine (free base)	2 mg/mL	500 mg	API	USP
		Excipient(s)		
Sodium Chloride	9 mg/mL	2250 mg/mL	Tonicity agent	USP/NF
Water for Injection	q.s 1/mL	q.s 250 mL	Solvent	USP

The inventors contemplate that additional ketamine products may be provided in different volumes with the same proportion of components as listed in Tables 1-4 above. Further, the inventors contemplate that other solvent systems may be substituted for the sodium chloride and water for injection. As one example, 5% dextrose in water for injection may be used in place of sodium chloride in water for injection in the formulations above. Further the inventors contemplate that any pharmaceutically acceptable salt of ketamine may be used in the formulations above, using the concentration of ketamine as the free base listed in Tables 3 and 4 above. The ketamine formulations above beneficially do not require an antimicrobial such as benzethonium chloride. The ketamine formulations above beneficially do not require any preservative. Nonetheless, the inventors contemplate that one or more excipients, such as a chelating or complexing agent or an antioxidant, may be added to the formulation without reducing the stability of the ready-to-use ketamine product described herein.

Example 2: Study of Stability Following Terminal Sterilization

Batches of the ketamine solution with the formulations described in Table 1 (1 mg/ml) and Table 2 (2 mg/ml) were manufactured to study the effect of terminal sterilization by autoclaving on product behavior. The primary packaging for each formulation included an infusion bag comprising a flexible multilayer film comprising a 3-layer polypropylene styrene-block copolymer based film (APP114S film manufactured by Polycine); a tube port comprising a multilayer polyolefin and styrene block copolymer tube material (APP107 manufactured by Polycine); and a twist off closure

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composed of low density polyethylene (LDPE) and polypropylene (PP). The closure comprised a membrane that created a barrier, wherein the inferior part of the membrane was in direct contact with the ketamine solution, while the superior part was in contact with a zone that forms an air chamber into the closure. Autoclaving of the primary packaging filled with the preservative-free ketamine formulations of Table 1 (1 mg/ml) and Table 2 (2 mg/ml), respectively, was conducted at a target temperature T=121° C.±1° C. and time at F0=15 according to USP <1222>, which is incorporated fully herein.

The objective of this study was to evaluate the quality of ketamine formulation seven days after the product is exposed to terminal sterilization processes at 121° C. at different F=0. Only slight, not significant, pH decrease was noted. There was no significant variation on assay (%) of ketamine from before to after sterilization.

TABLE 5

Assay and pH before vs after sterilization

	Product					
	Ketamine Formulation 1 mg/ml			Ketamine Formulation 2 mg/ml		
Batch	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Average Assay pre-sterilization (% of Ketamine base)	100.6	101.5	100.9	100.1	101.7	100.0
Assay post-sterilization (FP) (% of labelled amount of Ketamine base)	100.5	101.7	100.6	100.6	101.7	100.5
Extractable volume (ml)	251	252	251	252	251	252
Assay post-sterilization (FP) (% of Ketamine base)	100.1	100.9	100.2	99.8	101.3	99.7
Assay % change post- VS pre-sterilization	–0.5	–0.6	–0.7	–0.3	–0.4	–0.3
pH pre-sterilization (end of filling)	5.2	4.8	5.2	4.9	4.8	5.2
pH post-sterilization (FP)	4.6	4.5	4.6	4.6	4.4	4.7
Change in pH (post VS pre-sterilization)	–0.6	–0.3	–0.6	–0.3	–0.4	–0.5

For the ketamine product with the formulation described in Table 1 (1 mg/ml) the maximum pH decrease after sterilization was equal to 0.6 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.5 pH units.

For the ketamine product of the disclosure with the formulation described in Table 2 (2 mg/ml) the maximum pH decrease after sterilization was equal to 0.5 pH units which was in-line with results obtained on laboratory batches where decrease was equal to 0.4 pH units.

The results of Tables 5 show that the ketamine product of the invention can be terminally sterilized using autoclaving at a target temperature T=121° C.±1° C. and time at F0=15 according to USP <1222> without affecting the quality of ketamine formulation.

Example 3: Stability Studies

The terminally sterilized infusion bags, as described in Example 2, comprising a preservative-free aqueous ketamine solution with the formulation described in Table 1 (1 mg/ml) or Table 2 (2 mg/ml) were compared to a commercially available concentrated ketamine solution product in multi-dose glass vials containing the preservative benzethonium chloride. The commercially available concentrated products were diluted with 0.9% sodium chloride in a glass volumetric flask to achieve a concentration of 1 mg/mL or 2 mg/mL of Ketamine. The results for the 1 mg/ml and 2 mg/ml products are shown in Tables 6 and 7, respectively.

TABLE 6

Accelerated Condition 40 ± 2° C./<25% RH - 6 months

	Batch				
Test	Commercial Product Batch 1 (1 mg/mL)	Commercial Product Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 1 (1 mg/mL)	Ketamine Product of the Disclosure Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 3 (1 mg/mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	101.2	101.4	100.5	101.7	100.6

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TABLE 6-continued

	Accelerated Condition 40 ± 2° C./<25% RH - 6 months				
	Batch				
Test	Commercial Product Batch 1 (1 mg/mL)	Commercial Product Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 1 (1 mg/mL)	Ketamine Product of the Disclosure Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 3 (1 mg/mL)
Impurities:					
Specified identified impurity-Impurity A (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity B (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity C (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
pH (pH Units)	5.0	5.0	4.7	4.5	4.8
Osmolality (mOsmol/kg)	291	286	296	298	296

TABLE 7

	Accelerated Condition 40 ± 2° C./<25% RH - 6 months				
	Batch				
Test	Commercial Product Batch 1 (2 mg/mL)	Commercial Product Batch 2 (2 mg/mL)	Ketamine Product of the Disclosure Batch 1 (2 mg/mL)	Ketamine Product of the Disclosure Batch 2 (2 mg/mL)	Ketamine Product of the Disclosure Batch 3 (2 mg/mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.2	100.7	100.4	101.5	100.4
Impurities:					
Specified identified impurity-Impurity A (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity B (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity C (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.6
Osmolality (mOsmol/kg)	297	288	304	305	304

TABLE 8

Long term Condition 25 ± 2° C./40 ± 5% RH - 12 months					
	Batch				
Test	Commercial Product Batch 1 (1 mg/mL)	Commercial Product Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 1 (1 mg/mL)	Ketamine Product of the Disclosure Batch 2 (1 mg/mL)	Ketamine Product of the Disclosure Batch 3 (1 mg/mL)
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.9	102.1	100.5	101.9	100.7
Impurities:					
Specified identified impurity-Impurity A (%)	<0.05	<0.05	<0.05	0.05	0.06
Specified identified impurity-Impurity B (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity C (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurity (%)	<0.05	<0.05	<0.05	0.05	0.06
pH (pH Units)	5.1	5.0	4.8	4.5	4.8
Osmolality (mOsmol/kg)	287	290	293	294	295

TABLE 9

Long term Condition 25 ± 2° C./40 ± 5% RH - 12 months					
Batch	Commercial Product Batch 1 (2 mg/mL)	Commercial Product Batch 2 (2 mg/mL)	Ketamine Product of the Disclosure Batch 1 (2 mg/mL)	Ketamine Product of the Disclosure Batch 2 (2 mg/mL)	Ketamine Product of the Disclosure Batch 3 (2 mg/mL)
Test					
Appearance (Clear, colorless to slightly yellow, free from visible particle)	Comply	Comply	Comply	Comply	Comply
Assay (% labeled amount as ketamine)	100.3	102.3	100.5	101.7	100.6
Impurities:					
Specified identified impurity-Impurity A (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity B (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Specified identified impurity-Impurity C (%)	<0.05	<0.05	<0.05	<0.05	<0.05

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TABLE 9-continued

Long term Condition 25 ± 2° C./40 ± 5% RH - 12 months					
Batch Test Appearance	Commercial Product Batch 1 (2 mg/mL) Comply	Commercial Product Batch 2 (2 mg/mL) Comply	Ketamine Product of the Disclosure Batch 1 (2 mg/mL) Comply	Ketamine Product of the Disclosure Batch 2 (2 mg/mL) Comply	Ketamine Product of the Disclosure Batch 3 (2 mg/mL) Comply
Unspecified unidentified impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurity (%)	<0.05	<0.05	<0.05	<0.05	<0.05
pH (pH Units)	4.9	4.9	4.6	4.5	4.8
Osmolality (mOsmol/kg)	287	299	301	303	303

After 6 months of stability testing at 40° C., there was no observed variation in the pH and in the color of the ketamine products of the disclosure contained in ready-to-use, terminally sterilized, infusion bags. After 6 months at 40° C. there was no observed reduction in Ketamine Hydrochloride Assay compared to T=0 sterilized. The total impurities of the preservative-free ketamine formulations of the disclosure, packaged in ready-to-use, terminally sterilized, infusion bags were comparable with the results obtained at T=0.

The results of Tables 6-9 surprisingly show that the terminally sterilized ketamine products described herein, formulated without any antimicrobial, stabilizer or preservative, are at least as stable as the commercial formulation with benzethonium chloride under accelerated conditions and long-term storage. While the average pH of ketamine solution in infusion bags seen in the experiment was 4.5-4.8 pH units and the average pH of the commercially available product when diluted for use was 4.9-5.2, the ketamine solution in infusion bags remained stable. Additionally, osmolality of ketamine solution in infusion bags seen in the experiment was comparable to the commercially available product, and both were inside the physiological range (according to the USP <785>, which is incorporated fully herein, the osmolality of blood ranges between 285 and 310 mOsmol/kg) and therefore comparable in the context of this evaluation. No significant change was noted during the stability studies and no degradation was detected despite of a lack of any antimicrobial, stabilizer or preservative in the ketamine products of the present disclosure.

Example 4: Stress Studies

The ketamine product of the disclosure was analyzed to evaluate critical product characteristics/parameters under stressed conditions. Stress testing was intended to identify the likely degradation products, which further helped in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used.

An oxidative stress study was conducted in accordance with the procedure set out in FIG. **1**. The results for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:1 are shown in Tables 10 and 11, respectively, where "Δ" refers to the difference between the test batch and the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:1 ratio. The oxidative degradation 1:1 reported data was collected 72 hours after addition of the hydrogen peroxide.

TABLE 10

Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:1 with H_2O_2					
Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Completeness of Solution	Free from visible particles	—	Free from visible particles	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	Clear	—
pH	3.5-5.5	pH Units	4.74	4.58	–0.16
Osmolality	270-330	mOsmol/Kg	296	295	–1
Assay	95.0-105.0	%	100.0	99.6	–0.4
Impurities:					
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	0

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TABLE 10-continued

Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:1 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	0
Total impurities	NMT 1.0	%	<0.05	<0.05	0
Particulate matter:					
≥10 micron	NMT 23	No part/mL	0	0	0
≥25 micron	NMT 3		0	0	0

TABLE 11

Oxidative degradation results of ketamine solution 500 mg/250 mL (2 mg/ml) in ratio 1:1 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Completeness of Solution	Free from visible particles	—	Free from visible particles	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	Clear	—
pH	3.5-5.5	pH Units	4.60	4.56	–0.04
Osmolality	270-330	mOsmol/Kg	299	308	+9
Assay	95.0-105.0	%	99.7	99.6	–0.1
Impurities:					
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	0
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	0
Total impurities	NMT 1.0	%	<0.05	<0.05	0
Particulate matter:					
≥10 micron	NMT 23	No part/mL	0	0	0
≥25 micron	NMT 3		0	0	0

The results shown in Tables 10-11 demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed after 72 hours after the ketamine solution was treated with hydrogen peroxide in stoichiometric ratio 1:1.

The results of the oxidative stress for the 1 mg/mL and 2 mg/mL formulations (as described in Tables 1 and 2, respectively) treated with hydrogen peroxide in a ratio of 1:10 are shown in Tables 12 and 13, respectively, where "Δ" refers to the difference between the blank sample and Batch 1. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) without addition of hydrogen peroxide, while the "test batch" refers to the formulation with addition of hydrogen peroxide in a 1:10 ratio. The reported data was collected 48 hours after addition of the hydrogen peroxide.

TABLE 12

Oxidative degradation results of ketamine solution 250 mg/250 mL (1 mg/ml) in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (1 mg/ml)	Δ
Assay	95.0-105.0	%	100.2	99.2	–1.0
Impurities:					
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	0
Unspecified unidentified impurity RT 5.3	NMT 0.20	%	<0.05	0.13	+0.13
Unspecified unidentified impurity RT 9.0	NMT 0.20	%	<0.05	0.14	+0.14
Total impurities	NMT 1.0	%	<0.05	0.27	+0.27

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TABLE 13

Oxidative degradation results of ketamine solution 500 mg/250 mL in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Assay	95.0-105.0	%	100.1	99.5	–0.6
Impurities:					
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	0
Unspecified unidentified impurity RT 5.3	NMT 0.20	%	<0.05	0.08	0.08

TABLE 13-continued

Oxidative degradation results of ketamine solution 500 mg/250 mL in ratio 1:10 with H_2O_2

Test	Specifications	Unit	Blank sample	Test Batch (2 mg/ml)	Δ
Unspecified unidentified impurity RT 9.0	NMT 0.20	%	<0.05	0.08	0.08
Total impurities	NMT 1.0	%	<0.05	0.16	0.16

The results shown in Tables 12-13 demonstrate that there was a slight increase in impurities in the ketamine solution after 48 hours after the ketamine solution was treated with hydrogen peroxide in ratio 1:10.

An acid/alkaline study was conducted in accordance with the procedure set out in FIG. **2**. These results demonstrate that the ketamine product of the invention is stable, as no significant degradation of the ketamine solution was observed through one month of observation (t=1 M) compared to the blank sample. The "blank sample" refers to the formulation of Table 1 (1 mg/ml) or Table 2 (2 mg/ml) at pH 4.7, while the "test batch" refers to the formulation at varying test pH.

TABLE 14

Degradation results of ketamine solution 250 mg/250 mL at pH 2.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	NA*	pH Units	4.7	—	—	2.5	—
Osmolality	270-330	mOsmol/Kg	293	—	—	300	—
Assay	95.0-105.0	%	100.3	100.4	100.0	100.2	100.4
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

TABLE 15

Degradation results of ketamine solution 250 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—

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TABLE 15-continued

Degradation results of ketamine solution 250 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
pH	NA*	pH Units	4.7	—	—	3.5	—
Osmolality	270-330	mOsmol/Kg	293	—	—	294	—
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

TABLE 16

Degradation results of ketamine solution 250 mg/250 mL at pH 5.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	NA*	pH Units	4.7	—	—	3.5	—
Osmolality	270-330	mOsmol/Kg	293	—	—	294	—
Assay	95.0-105.0	%	100.2	100.1	100.2	100.1	100.2
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

TABLE 17

Degradation results of ketamine solution 250 mg/250 mL at pH 6.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—

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TABLE 17-continued

Degradation results of ketamine solution 250 mg/250 mL at pH 6.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
pH	NA*	pH Units	4.7	—	—	6.5	—
Osmolality	270-330	mOsmol/Kg	293	—	—	295	—
Assay	95.0-105.0	%	100.23	100.3	100.3	100.4	100.1
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

TABLE 18

Degradation results of ketamine solution 500 mg/250 mL at pH 2.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	3.5-5.5	pH Units	4.63	—	—	2.48	—
Osmolality	270-330	mOsmol/Kg	302	—	—	309	—
Assay	95.0-105.0	%	100.1	100.7	100.3	100.2	100.5
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

TABLE 19

Degradation results of ketamine solution 500 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—

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TABLE 19-continued

Degradation results of ketamine solution 500 mg/250 mL at pH 3.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	3.5-5.5	pH Units	4.63	—	—	3.51	—
Osmolality	270-330	mOsmol/Kg	302	—	—	305	—
Assay	95.0-105.0	%	100.1	100.4	100.1	100.0	100.1
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	1
≥25 micron	NMT 3		0	—	—	0	0

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TABLE 20

Degradation results of ketamine solution 500 mg/250 mL at pH 5.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	3.5-5.5	pH Units	4.63	—	—	5.51	—
Osmolality	270-330	mOsmol/Kg	302	—	—	303	—
Assay	95.0-105.0	%	100.1	100.2	100.2	100.2	100.1
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

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TABLE 21

Degradation results of ketamine solution 500 mg/250 mL at pH 6.5

Test	Specifications	Unit	Blank sample	t = 24 h	t = 48 h	t = 72 h	t = 1M
Completeness of Solution	Free from visible particles	—	Free from visible particles	—	—	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	—	—	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	—	—	Clear	—
pH	3.5-5.5	pH Units	4.63	—	—	6.50	—
Osmolality	270-330	mOsmol/Kg	302	—	—	304	—
Assay	95.0-105.0	%	100.1	100.0	100.2	100.1	100.2
			Impurities				
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	<0.05	<0.05
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	<0.05	<0.05
Particulate matter:							
≥10 micron	NMT 23	No part/mL	0	—	—	0	0
≥25 micron	NMT 3		0			0	0

A heat degradation study was performed on the ketamine solution in infusion bags in accordance to the procedure set out in FIG. **2**. The primary packaging used was the same infusion bags described in Example 2. No significant degradation of the ketamine solution in primary packaging was observed after two terminal sterilization cycles. The pH dropped slightly after each sterilization but it remained within the specification limits. These results demonstrate that the ketamine product of the invention is stable after two sterilization cycles conducted at 121° C. for 15 minutes each, as no significant change is noted in assay or impurity profile.

TABLE 22

Thermal stress results of Ketamine HCl Injection 250 mg/250 mL

Test	Specifications	Unit	Blank sample	Sterilization F015	Double sterilization F015	Δ
Completeness of Solution	Free from visible particles	—	Free from visible particles	Free from visible particles	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	Complies	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	Clear	Clear	—
pH	3.5-5.5	pH Units	4.7	4.5	4.3	–0.4
Osmolality	270-330	mOsmol/Kg	296	292	294	–2
Assay	95.0-105.0	%	100.0	99.5	98.9	–1.2
			Impurities			
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	0
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	0
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	0
Particulate matter:						
≥10 micron	NMT 23	No part/mL	0	0	1	+1
≥25 micron	NMT 3		0	0	0	0

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TABLE 23

Thermal stress results of Ketamine HCl Injection 500 mg/250 mL

Test	Specifications	Unit	Blank sample	Sterilization F015	Double sterilization F015	Δ
Completeness of Solution	Free from visible particles	—	Free from visible particles	Free from visible particles	Free from visible particles	—
Appearance of solution - Color	Colorless to slightly yellow	—	Complies	Complies	Complies	—
Appearance of solution - Clarity	Clear	—	Clear	Clear	Clear	—
pH	3.5-5.5	pH Units	4.6	4.3	4.1	–0.5
Osmolality	270-330	mOsmol/Kg	299	303	300	+1
Assay	95.0-105.0	%	99.7	99.4	99.0	–0.7
			Impurities			
Ketamine related compound A	NMT 0.20	%	<0.05	<0.05	<0.05	0
Unspecified unidentified impurity	NMT 0.20	%	<0.05	<0.05	<0.05	0
Total impurities	NMT 1.0	%	<0.05	<0.05	<0.05	0
Particulate matter:						
≥10 micron	NMT 23	No part/mL	0	0	1	+1
≥25 micron	NMT 3		0	0	0	0

Example 5: Manufacturing Process Development

The ketamine product of the disclosure is an aqueous solution and is terminally sterilized. The manufacturing process involved dissolution of ketamine HCl in water for injection and addition of sodium chloride to adjust for tonicity in accordance to the procedure set out in FIG. **4**.

Complete dissolution was verified by in process sampling and analysis of bulk solution before terminal sterilization as shown in FIGS. **5** and **6** and Table 23.

TABLE 23

Test results of Dissolution

				1 mg/mL (as in Table 1)			2 mg/mL (as in Table 2)		
Test	Limits	Units	Dissolution Time	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Appearance	Clear, colorless to slightly yellowish solution free from visible particles	n/a	5 min	comply	comply	comply	comply	comply	comply
			10 min	comply	comply	comply	comply	comply	comply
			15 min	comply	comply	comply	comply	comply	comply
pH	*	pH Units	5 min	5.0	4.8	5.3	5.1	4.8	5.2
			10 min	5.0	4.8	5.2	4.9	4.8	5.3
			15 min	5.0	4.7	5.2	5.0	4.8	5.2
Conductivity	14.3-15.3 (for information only)	mS/cm	5 min	15.3	15.3	15.3	15.1	15.1	15.0
			10 min	15.3	15.2	15.3	15.2	15.0	15.0
			15 min	15.3	15.2	15.3	14.7	15.0	14.9
Bulk solution Density	1.002-1.005 (for information only)	g/mL	5 min	n/a	n/a	n/a	n/a	n/a	n/a
			10 min	n/a	n/a	n/a	n/a	n/a	n/a
			15 min	1.004	1.004	1.004	1.004	1.004	1.004
Ketamine Assay	95.0-105.0	% of Ketamine base	5 min	101.9	101.6	100.9	100.7	102.0	100.0
			10 min	101.7	101.4	100.9	100.9	101.8	100.3
			15 min	101.8	101.4	100.9	100.6	102.3	100.1
Sodium Chloride Assay	146.0-162.0	mmol/L	5 min	156.9	153.7	154.9	155.9	155.8	154.5
			10 min	157.6	155.7	155.0	156.4	156.2	154.6
			15 min	157.2	156.3	154.6	155.5	156.1	154.7
Osmolality	270-330	mOsmol/kg	5 min	299	299	289	302	304	302
			10 min	301	293	293	302	305	302
			15 min	296	294	297	299	305	302

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The ketamine bulk solution was formulated as in Table 1 (1 mg/ml) and Table 2 (2 mg/ml) then filtered through a pre-filter (3 μm pore size) followed by a filtration through one filter (0.2 μm pore size filters). The in-line filtration was pressure driven (conducted under compressed air) and the drug product was then filled into infusion bags through the tube port in line with filtration. Drug product solution compatibility with the filter and robustness of the filling process was confirmed as shown in FIG. **7**.

TABLE 24

Filter Compatibility

Filling stop				1 mg/mL		2 mg/mL	
duration	Test	Limits	Units	Batch 1	Batch 2	Batch 4	Batch 5
1	pH	3.5-5.5	pH Units	5.3	4.7	4.9	4.8
Hour	(20-25° C.)			5.3	4.7	4.9	4.8
				5.3	4.7	4.9	4.8
	Ketamine	95.0-105.0	% of	100.7	101.5	99.9	101.3
	Assay		ketamine	100.6	101.6	100.0	101.7
			base	100.2	101.6	100.2	101.6
2	pH	3.5-5.5	pH Units	5.3	4.8	4.9	4.9
Hours	(20-25° C.)			5.3	4.8	4.9	4.8
				5.1	4.8	4.9	4.8
	Ketamine	95.0-105.0	% of	100.4	101.5	100.1	101.6
	Assay		ketamine	100.5	101.6	100.1	101.6
			base	100.3	101.4	100.1	101.5

After filling the infusion bag with the ketamine solution, the tube port was sealed using a twist-off closure. Terminal sterilization was then conducted using the autoclave process described in Example 2. The closure and tube port are thermally sealed due to the autoclave temperature.

These results demonstrate that the manufacturing process in accordance to the procedure shown in FIG. **4** is compatible with manufacturing the ketamine product of the invention as no significant change is noted in the characteristics of the ketamine solution (such as the ketamine assay, pH, etc.) during the dissolution and filtering steps.

It is to be understood that any particular aspect of the present disclosure that falls within the prior art may be excluded from any one or more of the claims. Since such aspects are deemed to be part of the whole of the present disclosure, any part of the whole disclosure may be excluded even if the exclusion is not set forth explicitly herein. Additionally, it is to be understood that while the present disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and alterations are within the scope of the following claims.

The invention claimed is:

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the ketamine product is sterile and ready-to-use (RTU), wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30° C.

2. The ketamine product of claim **1**, wherein the ketamine product has been terminally sterilized.

3. The ketamine product of claim **1**, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.

4. The ketamine product of claim **1**, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.

5. The ketamine product of claim **1**, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.

6. The ketamine product of claim **4**, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.

7. The ketamine product of claim **4**, wherein the closure comprises a plastic material.

8. The ketamine product of claim **4**, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

9. The ketamine product of claim **7**, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

10. The ketamine product of claim **4**, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

11. The ketamine product of claim **4**, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

12. The ketamine product of claim **4**, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises polypropylene styrene-block copolymer.

13. The ketamine product of claim **4**, wherein the infusion bag is contained within an overwrap.

14. The ketamine product of claim **13**, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

15. The ketamine product of claim **1**, wherein the ketamine product has been autoclaved.

16. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial

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free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30° C.

17. The ketamine product of claim **16**, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

18. The ketamine product of claim **1**, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at 25° C.±2° C. with relative humidity (RH) at 40%±5%.

19. The ketamine product of claim **1**, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at 40° C.±2° C./<25% RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25° C.±2° C./40% RH±5% RH is 97% or greater compared to the ketamine content before storage.

20. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim **1** to the subject as a continuous infusion.

21. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30° C.

22. The ketamine product of claim **16**, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at 25° C.±2° C. with relative humidity (RH) at 40%±5%.

23. The ketamine product of claim **21**, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at 25° C.±2° C. with relative humidity (RH) at 40%±5%.

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
SUITE 900 East
WASHINGTON, DC 20001

EXAMINER
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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Avenue, N.W.
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