

Exhibit B-2

Invalidity of U.S. Patent No. 11,878,076 in view of Nobelbar

Nobelbar qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of U.S. Patent No. 11,878,076 (“the ’076 Patent”), as discussed in greater detail in the chart that follows.¹ The citations below are to documents describing aspects of Nobelbar:

- *Deliberation Results Report: Nobelbar for intravenous injection 250 mg*, JAPAN EVALUATION AND LICENSING DIVISION, PHARMACEUTICAL AND FOOD SAFETY BUREAU (Sept. 16, 2008) (“Deliberation Results Report”) was published in 2008 and qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.
- Kou Kawada, *Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information*, 22(7) NEONATAL CARE 657 (2009) (“Kawada 2009”) was published in 2009 and qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.
- Kou Kawada et al., *A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures*, 42(4) JPN. J. CLIN. PHARMACOL. THER. 205 (2011) (“Kawada 2011”) was published in 2011 and qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.
- NOBELBAR® 250 mg for Injection Label (“Nobelbar Label”) was published and publicly available as of December 2008 and qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.

¹ Nothing in these claim charts should be construed as an admission regarding infringement, either literally or under the doctrine of equivalents, or as an admission regarding Sun’s understanding of the proper scope of the claims of the ’076 Patent. Given Plaintiff’s vague and ambiguous infringement contentions, the exemplary citations herein necessarily account for a variety of possible infringement arguments and claim constructions. Sun reserves the right to rely on additional citations or sources of evidence that also may be applicable, or that may become applicable in light of claim construction, changes in Plaintiff’s infringement contentions, and/or information obtained during discovery as the case progresses, including, but not limited to, third-party discovery related to any pharmaceutical product available at the time of the alleged invention. Various positions put forth in this document are predicated on Plaintiff’s overly broad interpretation of its claims as evidenced by the infringement allegations received to date. Those positions are not intended to and do not necessarily reflect Sun’s interpretation of the true and proper scope of Plaintiff’s claims, and Sun reserves the right to adopt claim construction positions that differ from or even conflict with various positions put forth in this document.

- *Pharmaceutical Interview Form of Nobelbar® 250 mg for intravenous infusion*, NOBELPHARMA CO., LTD. (Revised July 2010) (“PIF”) was publicly available as of March 13, 2011 and qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.
- Nobelpharma America documents bearing the bates range NOBEL-0001 - NOBEL-0205 (“Nobelbar Production”) describe Nobelbar 250 mg for Injection that was publicly available as of December 2008, which qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of the ’076 Patent.

Further discovery regarding Nobelbar, including, but not limited to, third-party discovery available at the time of the alleged invention, may also describe aspects of Nobelbar.

To the extent Plaintiff alleges that Nobelbar does not disclose any particular limitation of claims 1-20 of the ’076 Patent, either expressly or inherently, it would have been obvious to a person of ordinary skill in the art as of the priority date of the ’076 Patent to modify and/or to combine the teachings of Nobelbar, including but not limited to the prior art references presently found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section of charts for other prior art for the ’076 Patent in a manner that would have rendered the claims 1-20 invalid as obvious. The inclusion of the particular limitation into Nobelbar would have been obvious for at least the following reasons: It would have been obvious to modify Nobelbar, alone or in combination with the references identified in Section VII.B.2 of Sun’s Invalidity Contentions, to meet this limitation based on: (a) the teachings of Nobelbar itself; (b) a person of ordinary skill in the art implementing a predictable variation of Nobelbar or in the other identified references; (c) the logic, judgment, intelligence, creativity, innovation and common sense a person of ordinary skill in the art would employ; (d) the inferences and creative and routine steps that a person of ordinary skill in the art would employ; (e) market demand for pharmaceutical compositions and products to include this limitation; and/or (f) design needs or market pressures to solve a problem with a finite number of solutions that could have produced the desired outcome.

Sun reserves the right to amend or supplement this claim chart pursuant to the Docket Control Order issued by the Court on September 27, 2024 (Dkt. No. 37).

A. Claim 1

'076 Patent Claim Limitation	Nobelbar
[1p] A storage stable pharmaceutical product, comprising:	To the extent the preamble is limiting, Nobelbar discloses and/or renders obvious the preamble based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration

'076 Patent Claim Limitation	Nobelbar
	[Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus

'076 Patent Claim Limitation	Nobelbar
	15 - 20 mg/kg of phenobarbital is intravenously administered once daily • Deliberation Results Report at 3 Phenobarbital (PB), developed by Bayer AG (Germany) in 1912, is a typical barbiturate derivative with anticonvulsant, hypnotic, and sedative effects, and is widely used as a hypnotic, sedative, and seizure treatment for epilepsy in oral, injectable, and suppository formulations, and overseas, as of May 30, 2008, oral formulations of PB (tablets, oral solution, elixirs, sprays, syrups, etc.) are approved in 22 countries worldwide, including the U.S., the U.K., Germany, and France, and suppositories are approved in one country, Switzerland. Oral formulations of phenobarbital sodium (Clozapine) (tablets, oral solution, elixirs, sprays, and syrups) are approved in 3 countries, and injectable formulations are approved in 12 countries for intravenous injection, 13 countries for intramuscular injection, and 1 country for subcutaneous injection. In Japan, PB has been approved in tablets, powders, elixirs, and subcutaneous/intramuscular preparations since the approval of phenobal® powder in January 1944. Meanwhile, phenobarbital sodium (this drug) was approved for subcutaneous/intramuscular use in 1949, and a suppository was approved in March 1980. Oral drugs and subcutaneous/intramuscular preparations were notified of the results of the re-evaluation in June 1975, and the current indications (sedation of anxiety tone, autonomic seizures, psychomotor seizures, seizure of epilepsy) are described • Deliberation Results Report at 4 However, since there were issues such as the fact that the appropriate intravenous preparation was not marketed in Japan, the efficacy and effect of neonatal convulsions were not established, and the dosage and administration in children were not established except for suppositories, the clinical trial (investigator-initiated clinical trial) was initiated in March 2006 in which the investigator-initiated clinical trial was conducted. At this time, the Applicant believes that the efficacy and safety of the product for neonatal seizures have been confirmed based on the results of the investigator-initiated clinical trials and existing information, and with regard to status epilepticus, on November 24, 2005, the Japanese Pediatric Society and the Japanese Society of Pediatric Neurology submitted a request to the Minister of Health,

'076 Patent Claim Limitation	Nobelbar
	Labour and Welfare for an additional indication of intravenous phenobarbital for the treatment of status epilepticus. Based on this, the Applicant conducted a literature review, etc., and determined that the efficacy and safety of the drug for status epilepticus is widely recognized, and that the drug is known to medical and pharmaceutical authorities for status epilepticus, and submitted an application for approval for these two indications. Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature

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	and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. - PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" data-bbox="600 941 1667 1130"> <tr> <td data-bbox="600 941 1029 992">Dosage form</td><td data-bbox="1029 941 1667 992">Injection</td></tr> <tr> <td data-bbox="600 992 1029 1130">Standards / Content</td><td data-bbox="1029 992 1667 1130">Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 1	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Dosage form	Injection				
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'076 Patent Claim Limitation	Nobelbar
	I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus. I-2. Product features and efficacy 1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community. 2. It is the first drug indicated for neonatal seizures in Japan. 3. It can be administered to children and adults with status epilepticus. 4. This preparation does not contain any additives. 5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice) 6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval) 1. Since the most serious side effects may include Stevens-Johnsonsyndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored, If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted.

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	- PIF at 4 IV. Formulations IV-1. Dosage form - Dosage form classification, specifications and properties White mass or powder, lyophilized injection - pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) - Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation - Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) - additive not including - Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information - Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. - Kawada 2009 at 13

'076 Patent Claim Limitation	Nobelbar																
	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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	• Kawada 2011 at Title A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures • Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 µg/mL. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 205-06 In Japan, no phenobarbital preparation for intravenous injection was available despite an increasing demand for such product in neonatal care. An intravenous phenobarbital was discontinued in the 1980's, and Japanese neonatologists had no choice but to give intramuscular phenobarbital preparation intravenously or use imported intravenous phenobarbital products. Furthermore, due to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic

'076 Patent Claim Limitation	Nobelbar
	solvents such as benzyl alcohol and propylene glycol, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives. The Japan Pediatric Society (JPS) has been appealing to the Ministry of Health, Labour and Welfare (MHLW) for the medical need of appropriate phenobarbital preparations for neonatal seizures. The JPS finally succeeded in negotiating with Norbelpharma Co., Ltd. develop a new additive-free phenobarbital intravenous solution. Nobelpharma Co., Ltd. offered to supply an investigational drug in response to the appeal. This clinical trial, which was an investigator-initiated clinical trial, was funded by the MHLW and organized by physicians with the aim to obtain regulatory approval of the new phenobarbital preparation. • Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • Nobelbar Label

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	[Composition and Characteristics] <table border="1" data-bbox="600 329 1709 703"> <tr> <td data-bbox="600 329 936 375">Brand name</td><td data-bbox="936 329 1709 375">Nobelbar 250 mg for injection</td></tr> <tr> <td data-bbox="600 375 936 456">Ingredients and content</td><td data-bbox="936 375 1709 456">One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td data-bbox="600 456 936 501">Additives</td><td data-bbox="936 456 1709 501">None</td></tr> <tr> <td data-bbox="600 501 936 583">Formulation, color</td><td data-bbox="936 501 1709 583">White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td data-bbox="600 583 936 628">pH</td><td data-bbox="936 583 1709 628">9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td data-bbox="600 628 936 703">Ratio of osmotic pressure</td><td data-bbox="936 628 1709 703">2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0165-0167 To the extent Nobelbar does not expressly disclose the preamble, a person of ordinary skill in the art would have determined that the preamble is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of the preamble given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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[1a] a single use dose vial, and	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. See, e.g.: • Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium												

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	[Applicant] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg

'076 Patent Claim Limitation	Nobelbar
	[Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily • PIF at cover

'076 Patent Claim Limitation	Nobelbar				
	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">Dosage form</td><td style="text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> • PIF at 4 IV. Formulations	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
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'076 Patent Claim Limitation	Nobelbar
	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 10	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information - Kawada 2009 at Abstract

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	We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 13

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	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an

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	additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the patient's plasma drug concentration was confirmed to be below 40 μg/mL. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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	motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and

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	the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily - PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">Dosage form</td><td style="width: 50%; text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 4	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
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'076 Patent Claim Limitation	Nobelbar
	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at 13

'076 Patent Claim Limitation	Nobelbar																
	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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'076 Patent Claim Limitation	Nobelbar
	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the

'076 Patent Claim Limitation	Nobelbar												
	patient's plasma drug concentration was confirmed to be below 40 $\mu\text{g/mL}$. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - Nobelbar Label	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
Brand name	Nobelbar 250 mg for injection												
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'076 Patent Claim Limitation	Nobelbar
	[Dosage and Administration] Neonatal seizures Initial dose: Perform intravenous administration of 20 mg/kg as phenobarbital. If it is not possible to control the convulsions, the dose may be adjusted for additional intravenous administration according to the patient's condition within a range that does not exceed the initial dose used. Maintenance treatment: Perform intravenous administration of 2.5 ~ 5 mg/kg as phenobarbital once a day. Status epilepticus Perform intravenous administration of 15 ~ 20 mg/kg as phenobarbital once a day. To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[1c] wherein the composition is sterile and lyophilized, and	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant] Nobel Pharma K.K.

'076 Patent Claim Limitation	Nobelbar
	[Application date] September 14, 2007 [Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium

'076 Patent Claim Limitation	Nobelbar
	[Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily • Deliberation Results Report at 3 Phenobarbital (PB), developed by Bayer AG (Germany) in 1912, is a typical barbiturate derivative with anticonvulsant, hypnotic, and sedative effects, and is widely used as a hypnotic, sedative, and seizure treatment for epilepsy in oral, injectable, and suppository formulations, and overseas, as of May 30, 2008, oral formulations of PB (tablets, oral solution, elixirs, sprays, syrups, etc.) are approved in 22 countries worldwide, including the U.S., the U.K., Germany, and France, and suppositories are approved in one country, Switzerland. Oral formulations of phenobarbital sodium (Clozapine) (tablets,

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	oral solution, elixirs, sprays, and syrups) are approved in 3 countries, and injectable formulations are approved in 12 countries for intravenous injection, 13 countries for intramuscular injection, and 1 country for subcutaneous injection. In Japan, PB has been approved in tablets, powders, elixirs, and subcutaneous/intramuscular preparations since the approval of phenobar® powder in January 1944. Meanwhile, phenobarbital sodium (this drug) was approved for subcutaneous/intramuscular use in 1949, and a suppository was approved in March 1980. Oral drugs and subcutaneous/intramuscular preparations were notified of the results of the re-evaluation in June 1975, and the current indications (sedation of anxiety tone, autonomic seizures, psychomotor seizures, seizure of epilepsy) are described • Deliberation Results Report at 4 However, since there were issues such as the fact that the appropriate intravenous preparation was not marketed in Japan, the efficacy and effect of neonatal convulsions were not established, and the dosage and administration in children were not established except for suppositories, the clinical trial (investigator-initiated clinical trial) was initiated in March 2006 in which the investigator-initiated clinical trial was conducted. At this time, the Applicant believes that the efficacy and safety of the product for neonatal seizures have been confirmed based on the results of the investigator-initiated clinical trials and existing information, and with regard to status epilepticus, on November 24, 2005, the Japanese Pediatric Society and the Japanese Society of Pediatric Neurology submitted a request to the Minister of Health, Labour and Welfare for an additional indication of intravenous phenobarbital for the treatment of status epilepticus. Based on this, the Applicant conducted a literature review, etc., and determined that the efficacy and safety of the drug for status epilepticus is widely recognized, and that the drug is known to medical and pharmaceutical authorities for status epilepticus, and submitted an application for approval for these two indications. • Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a

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	longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. • Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. • PIF at cover

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	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">Dosage form</td><td style="text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> • PIF at 1	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Dosage form	Injection				
Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)				

'076 Patent Claim Limitation	Nobelbar
	I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus. I-2. Product features and efficacy 1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community. 2. It is the first drug indicated for neonatal seizures in Japan. 3. It can be administered to children and adults with status epilepticus. 4. This preparation does not contain any additives. 5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice) 6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval) 1. Since the most serious side effects may include Stevens-Johnsonsyndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored, If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted.

'076 Patent Claim Limitation	Nobelbar
	- PIF at 4 IV. Formulations IV-1. Dosage form - Dosage form classification, specifications and properties White mass or powder, lyophilized injection - pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) - Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation - Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) - additive not including

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. • Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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'076 Patent Claim Limitation	Nobelbar
	• Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0021; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[1d] wherein the composition comprises no less than 98% phenobarbital	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i>

'076 Patent Claim Limitation	Nobelbar
sodium.	• Deliberation Results Report at 5 The drug product is a lyophilized injection composed of drug substance only, without additives, with a clear colorless glass vial/rubber stopper/flip cap applied to the container and closure system. An application has been submitted for a formulation containing 274 mg of phenobarbital sodium (250 mg of phenobarbital) per vial. In drug product development, phenobarbital is extremely slightly soluble in water, and the use of a soluble supplement was considered to be unfavorable for neonates. Therefore, it is considered appropriate to use high water solubility of phenobarbital sodium as the drug substance, no additive, and to use the formulation as a lyophilized injection. • PIF at 1 I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus.

'076 Patent Claim Limitation	Nobelbar
	I-2. Product features and efficacy 1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community. 2. It is the first drug indicated for neonatal seizures in Japan. 3. It can be administered to children and adults with status epilepticus. 4. This preparation does not contain any additives. 5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice) 6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval) 1. Since the most serious side effects may include Stevens-Johnsonsyndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored, If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted. • PIF at 4 IV. Formulations

'076 Patent Claim Limitation	Nobelbar
	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including • Kawada 2009 at 12 However, the following problems were present. In Japan, phenobarbital preparations are not commercially available for intravenous administration, and intramuscular and subcutaneous preparations are being used for intravenous administration. It is administered even though the package insert states that “do not administer intravenously” 5). The description in the package insert for this is as follows: “Because this drug precipitates the main drug with water, it should not be injected intravenously or mixed with other injected drugs” for 10% phenobarbital® and “intravenous injection” for 10% phenobarbital injection “Marco”. Avoid mixing with other injections and use them separately. “ Although 10% Phenobarbital® for intramuscular injection contains organic solvents such as chlorobutanol and glycerin diethylether as additives in order to dissolve a poorly soluble main drug, administration of 10% phenobarbital for injection “Marco” containing benzyl alcohol, which is a similar organic solvent, is considered to be associated with the gasping syndrome due to benzyl alcohol toxicity, and when possible, it is preferable to use a drug product that does not contain these additives especially in newborns and low birth weight infants. • Kawada 2009 at 13

'076 Patent Claim Limitation	Nobelbar
	For phenobarbital sodium preparations approved for intravenous administration overseas, organic solvents such as propylene glycol and alcohol are also used. In addition, it is known that turbidity occurs when diluting 10% Phenobarbital®, an intramuscular injection product in Japan, for intravenous injection, and its safety may be problematic. In this way, early development of intravenous preparations containing no additives in Japan has been strongly desired by academic societies (Japan Society for Premature and Newborn Medicine, the Japanese Society of Child Neurology, etc.). • Kawada 2011 at Title A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures • Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal

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	seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Kawada 2011 at 205-06 In Japan, no phenobarbital preparation for intravenous injection was available despite an increasing demand for such product in neonatal care. An intravenous phenobarbital was discontinued in the 1980's, and Japanese neonatologists had no choice but to give intramuscular phenobarbital preparation intravenously or use imported intravenous phenobarbital products. Furthermore, due to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic solvents such as benzyl alcohol and propylene glycol, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives. The Japan Pediatric Society (JPS) has been appealing to the Ministry of Health, Labour and Welfare (MHLW) for the medical need of appropriate phenobarbital preparations for neonatal seizures. The JPS finally succeeded in negotiating with Norbelpharma Co., Ltd. develop a new additive-free phenobarbital intravenous solution. Nobelpharma Co., Ltd. offered to supply an investigational drug in response to the appeal. This clinical trial, which was an investigator-initiated clinical trial, was funded by the MHLW and organized by physicians with the aim to obtain regulatory approval of the new phenobarbital preparation. • Kawada 2011 at 209 This study was performed to evaluate the new injectable phenobarbital preparation containing no additives for the treatment of neonatal seizures. • Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is

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	effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - See generally Nobelbar Production; see, e.g., NOBEL-0081-0092 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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'076 Patent Claim Limitation	Nobelbar
	very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

B. Claim 2

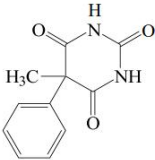
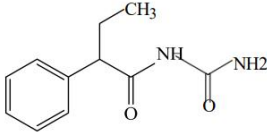
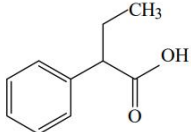
'076 Patent Claim Limitation	Nobelbar
[2p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> - Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. - Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these

'076 Patent Claim Limitation	Nobelbar																
	tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. - PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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'076 Patent Claim Limitation	Nobelbar
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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks																					

'076 Patent Claim Limitation	Nobelbar																																																														
	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
Test item	Storage period																																																														
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'076 Patent Claim Limitation	Nobelbar
	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows  5-methyl-5-phenyl-barbituric acid Analogues that may be generated in the formulation manufacturing process are as follows  2-phenylbutyrylurea or  2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

C. Claim 3

'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[3p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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'076 Patent Claim Limitation	Nobelbar																																																														
	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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'076 Patent Claim Limitation	Nobelbar
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D. Claim 4

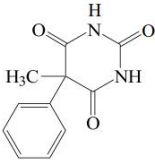
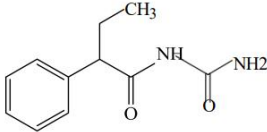
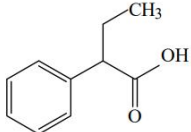
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[4p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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'076 Patent Claim Limitation	Nobelbar
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E. Claim 5

'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[5p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[5a] wherein the composition is amorphous.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • PIF at cover

'076 Patent Claim Limitation	Nobelbar
	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. • PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar
	• Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information • Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0203-0205; NOBEL-0203 (Fig. 5) To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

F. Claim 6

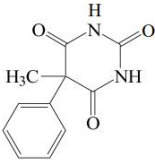
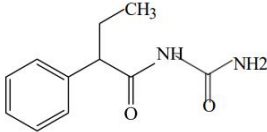
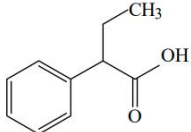
'076 Patent Claim Limitation	Nobelbar
[6p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. • Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were

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	observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. - PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
Type of test	Storage conditions	Storage method	Storage period														
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Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months														

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	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows  5-methyl-5-phenyl-barbitaric acid Analogues that may be generated in the formulation manufacturing process are as follows  2-phenylbutyrylurea or  2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

G. Claim 7

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[7p] A pharmaceutical product, comprising:	To the extent the preamble is limiting, Nobelbar discloses and/or renders obvious the preamble based on at least the following citations. <i>See, e.g.:</i> - Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug - Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III

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	• Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily

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	• Deliberation Results Report at 3 Phenobarbital (PB), developed by Bayer AG (Germany) in 1912, is a typical barbiturate derivative with anticonvulsant, hypnotic, and sedative effects, and is widely used as a hypnotic, sedative, and seizure treatment for epilepsy in oral, injectable, and suppository formulations, and overseas, as of May 30, 2008, oral formulations of PB (tablets, oral solution, elixirs, sprays, syrups, etc.) are approved in 22 countries worldwide, including the U.S., the U.K., Germany, and France, and suppositories are approved in one country, Switzerland. Oral formulations of phenobarbital sodium (Clozapine) (tablets, oral solution, elixirs, sprays, and syrups) are approved in 3 countries, and injectable formulations are approved in 12 countries for intravenous injection, 13 countries for intramuscular injection, and 1 country for subcutaneous injection. In Japan, PB has been approved in tablets, powders, elixirs, and subcutaneous/intramuscular preparations since the approval of phenobarbital® powder in January 1944. Meanwhile, phenobarbital sodium (this drug) was approved for subcutaneous/intramuscular use in 1949, and a suppository was approved in March 1980. Oral drugs and subcutaneous/intramuscular preparations were notified of the results of the re-evaluation in June 1975, and the current indications (sedation of anxiety tone, autonomic seizures, psychomotor seizures, seizure of epilepsy) are described • Deliberation Results Report at 4 However, since there were issues such as the fact that the appropriate intravenous preparation was not marketed in Japan, the efficacy and effect of neonatal convulsions were not established, and the dosage and administration in children were not established except for suppositories, the clinical trial (investigator-initiated clinical trial) was initiated in March 2006 in which the investigator-initiated clinical trial was conducted. At this time, the Applicant believes that the efficacy and safety of the product for neonatal seizures have been confirmed based on the results of the investigator-initiated clinical trials and existing information, and with regard to status epilepticus, on November 24, 2005, the Japanese Pediatric Society and the Japanese Society of Pediatric Neurology submitted a request to the Minister of Health, Labour and Welfare for an additional indication of intravenous phenobarbital for the treatment of status epilepticus. Based on this, the Applicant conducted a literature review, etc., and determined that the

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	efficacy and safety of the drug for status epilepticus is widely recognized, and that the drug is known to medical and pharmaceutical authorities for status epilepticus, and submitted an application for approval for these two indications. • Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. • Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

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	- PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">Dosage form</td><td style="text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 1	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Dosage form	Injection				
Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)				

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	I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus. I-2. Product features and efficacy 1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community. 2. It is the first drug indicated for neonatal seizures in Japan. 3. It can be administered to children and adults with status epilepticus. 4. This preparation does not contain any additives. 5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice) 6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval) 1. Since the most serious side effects may include Stevens-Johnsonsyndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored, If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted.

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	- PIF at 4 IV. Formulations IV-1. Dosage form - Dosage form classification, specifications and properties White mass or powder, lyophilized injection - pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) - Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation - Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) - additive not including - Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information - Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. - Kawada 2009 at 13

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	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.																

'076 Patent Claim Limitation	Nobelbar
	• Kawada 2011 at Title A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures • Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 µg/mL. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 205-06 In Japan, no phenobarbital preparation for intravenous injection was available despite an increasing demand for such product in neonatal care. An intravenous phenobarbital was discontinued in the 1980's, and Japanese neonatologists had no choice but to give intramuscular phenobarbital preparation intravenously or use imported intravenous phenobarbital products. Furthermore, due to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic

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	solvents such as benzyl alcohol and propylene glycol, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives. The Japan Pediatric Society (JPS) has been appealing to the Ministry of Health, Labour and Welfare (MHLW) for the medical need of appropriate phenobarbital preparations for neonatal seizures. The JPS finally succeeded in negotiating with Norbelpharma Co., Ltd. develop a new additive-free phenobarbital intravenous solution. Nobelpharma Co., Ltd. offered to supply an investigational drug in response to the appeal. This clinical trial, which was an investigator-initiated clinical trial, was funded by the MHLW and organized by physicians with the aim to obtain regulatory approval of the new phenobarbital preparation. • Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • Nobelbar Label

'076 Patent Claim Limitation	Nobelbar												
	[Composition and Characteristics] <table border="1" data-bbox="600 329 1709 703"> <tr> <td data-bbox="600 329 936 375">Brand name</td><td data-bbox="936 329 1709 375">Nobelbar 250 mg for injection</td></tr> <tr> <td data-bbox="600 375 936 456">Ingredients and content</td><td data-bbox="936 375 1709 456">One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td data-bbox="600 456 936 501">Additives</td><td data-bbox="936 456 1709 501">None</td></tr> <tr> <td data-bbox="600 501 936 583">Formulation, color</td><td data-bbox="936 501 1709 583">White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td data-bbox="600 583 936 628">pH</td><td data-bbox="936 583 1709 628">9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td data-bbox="600 628 936 703">Ratio of osmotic pressure</td><td data-bbox="936 628 1709 703">2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> • See generally Nobelbar Production To the extent Nobelbar does not expressly disclose the preamble, a person of ordinary skill in the art would have determined that the preamble is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of the preamble given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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[7a] a single use dose vial, and	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. See, e.g.: • Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant] Nobel Pharma K.K. [Application date] September 14, 2007												

'076 Patent Claim Limitation	Nobelbar
	[Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K.

'076 Patent Claim Limitation	Nobelbar
	[Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily • PIF at cover

'076 Patent Claim Limitation	Nobelbar				
	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">Dosage form</td><td style="width: 50%;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> • PIF at 4 IV. Formulations	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Dosage form	Injection				
Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)				

'076 Patent Claim Limitation	Nobelbar
	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 10	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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'076 Patent Claim Limitation	Nobelbar
	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information - Kawada 2009 at Abstract

'076 Patent Claim Limitation	Nobelbar
	We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 13

'076 Patent Claim Limitation	Nobelbar																
	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an

'076 Patent Claim Limitation	Nobelbar												
	additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the patient's plasma drug concentration was confirmed to be below 40 μg/mL. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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'076 Patent Claim Limitation	Nobelbar
	motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and

'076 Patent Claim Limitation	Nobelbar				
	the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily - PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">Dosage form</td><td style="width: 50%; text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 4	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Dosage form	Injection				
Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)				

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	IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 10	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at 13

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	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.																

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	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the

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	patient's plasma drug concentration was confirmed to be below 40 $\mu\text{g/mL}$. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - Nobelbar Label	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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	[Dosage and Administration] Neonatal seizures Initial dose: Perform intravenous administration of 20 mg/kg as phenobarbital. If it is not possible to control the convulsions, the dose may be adjusted for additional intravenous administration according to the patient's condition within a range that does not exceed the initial dose used. Maintenance treatment: Perform intravenous administration of 2.5 ~ 5 mg/kg as phenobarbital once a day. Status epilepticus Perform intravenous administration of 15 ~ 20 mg/kg as phenobarbital once a day. To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[7c] wherein the composition is sterile and lyophilized,	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at cover [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant] Nobel Pharma K.K.

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	[Application date] September 14, 2007 [Review results] At the First Committee of Pharmaceutical Preparations held on August 29, 2008, it was judged that approval of this item was no problem, and it was decided to report this to the Pharmaceutical Affairs Section of the Pharmaceutical Affairs and Food and Hygiene Council. This item does not fall under biological products or specified biological products, and the reexamination period is 10 years for neonatal convulsions and 6 years for status epilepticus, and both the drug substance and drug product are considered to fall under the powerful drug • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium

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	[Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily • Deliberation Results Report at 3 Phenobarbital (PB), developed by Bayer AG (Germany) in 1912, is a typical barbiturate derivative with anticonvulsant, hypnotic, and sedative effects, and is widely used as a hypnotic, sedative, and seizure treatment for epilepsy in oral, injectable, and suppository formulations, and overseas, as of May 30, 2008, oral formulations of PB (tablets, oral solution, elixirs, sprays, syrups, etc.) are approved in 22 countries worldwide, including the U.S., the U.K., Germany, and France, and suppositories are approved in one country, Switzerland. Oral formulations of phenobarbital sodium (Clozapine) (tablets,

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	oral solution, elixirs, sprays, and syrups) are approved in 3 countries, and injectable formulations are approved in 12 countries for intravenous injection, 13 countries for intramuscular injection, and 1 country for subcutaneous injection. In Japan, PB has been approved in tablets, powders, elixirs, and subcutaneous/intramuscular preparations since the approval of phenobar® powder in January 1944. Meanwhile, phenobarbital sodium (this drug) was approved for subcutaneous/intramuscular use in 1949, and a suppository was approved in March 1980. Oral drugs and subcutaneous/intramuscular preparations were notified of the results of the re-evaluation in June 1975, and the current indications (sedation of anxiety tone, autonomic seizures, psychomotor seizures, seizure of epilepsy) are described • Deliberation Results Report at 4 However, since there were issues such as the fact that the appropriate intravenous preparation was not marketed in Japan, the efficacy and effect of neonatal convulsions were not established, and the dosage and administration in children were not established except for suppositories, the clinical trial (investigator-initiated clinical trial) was initiated in March 2006 in which the investigator-initiated clinical trial was conducted. At this time, the Applicant believes that the efficacy and safety of the product for neonatal seizures have been confirmed based on the results of the investigator-initiated clinical trials and existing information, and with regard to status epilepticus, on November 24, 2005, the Japanese Pediatric Society and the Japanese Society of Pediatric Neurology submitted a request to the Minister of Health, Labour and Welfare for an additional indication of intravenous phenobarbital for the treatment of status epilepticus. Based on this, the Applicant conducted a literature review, etc., and determined that the efficacy and safety of the drug for status epilepticus is widely recognized, and that the drug is known to medical and pharmaceutical authorities for status epilepticus, and submitted an application for approval for these two indications. • Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a

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	longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. • Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. • PIF at cover

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	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">Dosage form</td><td style="text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> • PIF at 1	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
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Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)				

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	I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus. I-2. Product features and efficacy 1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community. 2. It is the first drug indicated for neonatal seizures in Japan. 3. It can be administered to children and adults with status epilepticus. 4. This preparation does not contain any additives. 5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice) 6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval) 1. Since the most serious side effects may include Stevens-Johnsonsyndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored, If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted.

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	- PIF at 4 IV. Formulations IV-1. Dosage form - Dosage form classification, specifications and properties White mass or powder, lyophilized injection - pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) - Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation - Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) - additive not including

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. • Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	• Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0021; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[7d] wherein the composition comprises no less than 98% phenobarbital	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i>

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sodium, and	• Deliberation Results Report at 5 The drug product is a lyophilized injection composed of drug substance only, without additives, with a clear colorless glass vial/rubber stopper/flip cap applied to the container and closure system. An application has been submitted for a formulation containing 274 mg of phenobarbital sodium (250 mg of phenobarbital) per vial. In drug product development, phenobarbital is extremely slightly soluble in water, and the use of a soluble supplement was considered to be unfavorable for neonates. Therefore, it is considered appropriate to use high water solubility of phenobarbital sodium as the drug substance, no additive, and to use the formulation as a lyophilized injection. • PIF at 1 I-1. History of development Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide. Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories. On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005. In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus.

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'076 Patent Claim Limitation	Nobelbar
	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including • Kawada 2009 at 12 However, the following problems were present. In Japan, phenobarbital preparations are not commercially available for intravenous administration, and intramuscular and subcutaneous preparations are being used for intravenous administration. It is administered even though the package insert states that “do not administer intravenously” 5). The description in the package insert for this is as follows: “Because this drug precipitates the main drug with water, it should not be injected intravenously or mixed with other injected drugs” for 10% phenobarbital® and “intravenous injection” for 10% phenobarbital injection “Marco”. Avoid mixing with other injections and use them separately. “ Although 10% Phenobarbital® for intramuscular injection contains organic solvents such as chlorobutanol and glycerin diethylether as additives in order to dissolve a poorly soluble main drug, administration of 10% phenobarbital for injection “Marco” containing benzyl alcohol, which is a similar organic solvent, is considered to be associated with the gasping syndrome due to benzyl alcohol toxicity, and when possible, it is preferable to use a drug product that does not contain these additives especially in newborns and low birth weight infants. • Kawada 2009 at 13

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	For phenobarbital sodium preparations approved for intravenous administration overseas, organic solvents such as propylene glycol and alcohol are also used. In addition, it is known that turbidity occurs when diluting 10% Phenobarbital®, an intramuscular injection product in Japan, for intravenous injection, and its safety may be problematic. In this way, early development of intravenous preparations containing no additives in Japan has been strongly desired by academic societies (Japan Society for Premature and Newborn Medicine, the Japanese Society of Child Neurology, etc.). • Kawada 2011 at Title A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures • Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal

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	seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Kawada 2011 at 205-06 In Japan, no phenobarbital preparation for intravenous injection was available despite an increasing demand for such product in neonatal care. An intravenous phenobarbital was discontinued in the 1980's, and Japanese neonatologists had no choice but to give intramuscular phenobarbital preparation intravenously or use imported intravenous phenobarbital products. Furthermore, due to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic solvents such as benzyl alcohol and propylene glycol, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives. The Japan Pediatric Society (JPS) has been appealing to the Ministry of Health, Labour and Welfare (MHLW) for the medical need of appropriate phenobarbital preparations for neonatal seizures. The JPS finally succeeded in negotiating with Norbelpharma Co., Ltd. develop a new additive-free phenobarbital intravenous solution. Nobelpharma Co., Ltd. offered to supply an investigational drug in response to the appeal. This clinical trial, which was an investigator-initiated clinical trial, was funded by the MHLW and organized by physicians with the aim to obtain regulatory approval of the new phenobarbital preparation. • Kawada 2011 at 209 This study was performed to evaluate the new injectable phenobarbital preparation containing no additives for the treatment of neonatal seizures. • Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is

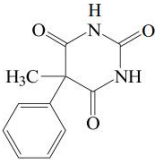
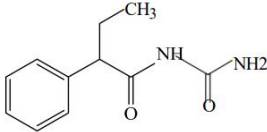
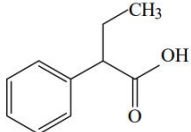
'076 Patent Claim Limitation	Nobelbar												
	effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - See generally Nobelbar Production; see, e.g., NOBEL-0081-0092 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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	very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.
[7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as "tight container, room temperature storage" and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

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	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows  5-methyl-5-phenyl-barbituric acid Analogues that may be generated in the formulation manufacturing process are as follows  2-phenylbutyrylurea or  2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

H. Claim 8

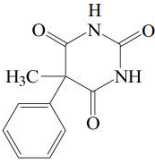
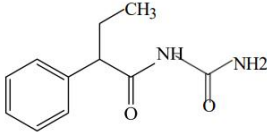
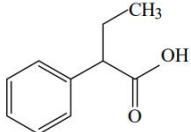
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[8p] The pharmaceutical product of claim 7,	<i>See supra</i> Claim 7.
[8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months														

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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I. Claim 9

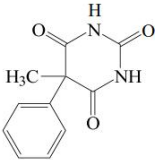
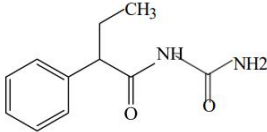
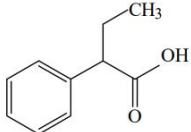
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[9p] The pharmaceutical product of claim 7,	See <i>supra</i> Claim 7.
[9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. See, e.g.: Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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J. Claim 10

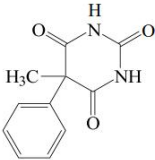
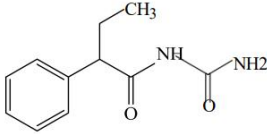
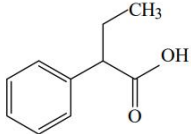
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[10p] The pharmaceutical product of claim 7,	<i>See supra</i> Claim 7.
[10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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K. Claim 11

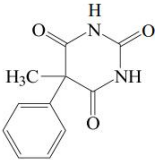
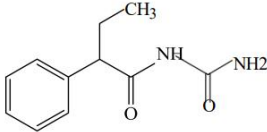
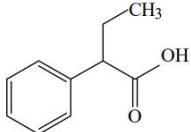
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[11p] The pharmaceutical product of claim 10,	See <i>supra</i> Claim 10.
[11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. See, e.g.: Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
Type of test	Storage conditions	Storage method	Storage period														
Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months														
Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months														
Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months														

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
Type of test	Storage conditions	Storage method	Storage period																					
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	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks																					

'076 Patent Claim Limitation	Nobelbar																																																														
	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
Test item	Storage period																																																														
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	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows  5-methyl-5-phenyl-barbitaric acid Analogues that may be generated in the formulation manufacturing process are as follows  2-phenylbutyrylurea or  2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

L. Claim 12

'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[12p] The pharmaceutical product of claim 7,	<i>See supra</i> Claim 7.
[12a] wherein the composition is amorphous.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • PIF at cover

'076 Patent Claim Limitation	Nobelbar
	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. • PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar
	• Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information • Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0203-0205; NOBEL-0203 (Fig. 5) To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

M. Claim 13

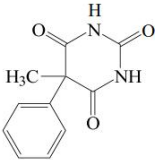
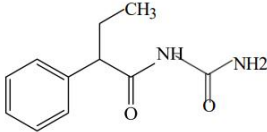
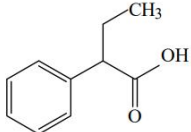
'076 Patent Claim Limitation	Nobelbar
[13p] The pharmaceutical product of claim 12,	<i>See supra</i> Claim 12.
[13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were

'076 Patent Claim Limitation	Nobelbar																
	observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. - PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months														
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	IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
Type of test	Storage conditions	Storage method	Storage period																					
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'076 Patent Claim Limitation	Nobelbar																																																														
	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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'076 Patent Claim Limitation	Nobelbar
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N. Claim 14

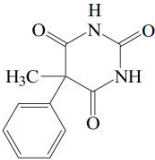
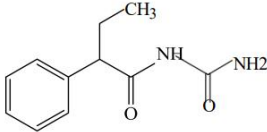
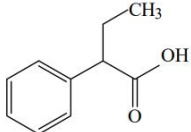
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[14p] The pharmaceutical product of claim 1,	See <i>supra</i> Claim 1.
[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. See, e.g.: Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
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'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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'076 Patent Claim Limitation	Nobelbar
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O. Claim 15

'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[15p] The pharmaceutical product of claim 14,	<i>See supra</i> Claim 14.
[15a] wherein the composition is amorphous.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • PIF at cover

'076 Patent Claim Limitation	Nobelbar
	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. • PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar
	• Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information • Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0203-0205; NOBEL-0203 (Fig. 5) To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

P. Claim 16

'076 Patent Claim Limitation	Nobelbar
[16p] The pharmaceutical product of claim 1,	<i>See supra</i> Claim 1.
[16a] wherein the product comprises the 100 mg dose in the single use dose vial.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and

'076 Patent Claim Limitation	Nobelbar				
	the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus 15 - 20 mg/kg of phenobarbital is intravenously administered once daily - PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">Dosage form</td><td style="width: 50%; text-align: center;">Injection</td></tr> <tr> <td style="text-align: center;">Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 4	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
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	IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 10	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at 13

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	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
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'076 Patent Claim Limitation	Nobelbar
	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the

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	patient's plasma drug concentration was confirmed to be below 40 $\mu\text{g/mL}$. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - Nobelbar Label	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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	[Dosage and Administration] Neonatal seizures Initial dose: Perform intravenous administration of 20 mg/kg as phenobarbital. If it is not possible to control the convulsions, the dose may be adjusted for additional intravenous administration according to the patient's condition within a range that does not exceed the initial dose used. Maintenance treatment: Perform intravenous administration of 2.5 ~ 5 mg/kg as phenobarbital once a day. Status epilepticus Perform intravenous administration of 15 ~ 20 mg/kg as phenobarbital once a day. To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

Q. Claim 17

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[17p] The pharmaceutical product of claim 7,	<i>See supra</i> Claim 7.

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[17a] wherein the product comprises the 100 mg dose in the single use dose vial.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 2 Review results August 11, 2008 [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Review results] Based on the submitted materials, it is considered that the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated. For neonatal convulsions and status epilepticus, further investigation is considered necessary in post-marketing surveillance regarding the relationship between the administration status (dose, administration rate) of the drug and safety and efficacy, the relationship between blood concentration and safety and efficacy, and the occurrence of serious skin disorders. As a result of the review by the Pharmaceuticals and Medical Devices Agency, it was determined that the following indications and dosage and administration were approved for this item. [Indications] Neonatal convulsion, status epilepticus [Dosage and administration] Neonatal convulsion Initial dose: 20 mg/kg intravenously as phenobarbital. If convulsions cannot be controlled, the dose should be adjusted to the extent not exceeding the initial dose, depending on the patient's condition, and the dose should be additionally administered intravenously. Maintenance dose: 2.5 - 5 mg/kg of phenobarbital is intravenously administered once daily. Status epilepticus

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	15 - 20 mg/kg of phenobarbital is intravenously administered once daily - PIF at cover Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. <table border="1"> <tr> <td>Dosage form</td><td>Injection</td></tr> <tr> <td>Standards / Content</td><td>Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)</td></tr> </table> - PIF at 4 IV. Formulations	Dosage form	Injection	Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
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'076 Patent Claim Limitation	Nobelbar
	V-2. Dosage and administration Neonatal seizure Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily. - PIF at 39 Approved indications for this drug Neonatal seizures Status epilepticus Approved dosage and administration of this drug Neonatal seizures Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously. Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily. Status epilepticus Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily. - Kawada 2009 at 13

'076 Patent Claim Limitation	Nobelbar																
	Table NOBELBAR® Overview <table> <tr> <td>Brand name:</td><td>NOBELBAR® 250mg for intravenous injection</td></tr> <tr> <td>Ingredient and content</td><td>274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)</td></tr> <tr> <td>Additive</td><td>None</td></tr> <tr> <td>pH</td><td>9.2 to 10.2 (when 1g is dissolved in 10mL of water)</td></tr> <tr> <td>Osmotic pressure ratio</td><td>2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)</td></tr> <tr> <td>Indications</td><td>Neonatal convulsion/ status epilepticus</td></tr> <tr> <td>Dosage and administration (Neonatal convulsion)</td><td>Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.</td></tr> <tr> <td>Usage precautions</td><td>Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.</td></tr> </table>	Brand name:	NOBELBAR® 250mg for intravenous injection	Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)	Additive	None	pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)	Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)	Indications	Neonatal convulsion/ status epilepticus	Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.	Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.
Brand name:	NOBELBAR® 250mg for intravenous injection																
Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)																
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Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.																

'076 Patent Claim Limitation	Nobelbar
	• Kawada 2011 at Abstract Aims: A new phenobarbital preparation for injection containing no additives (NOBELBAR®) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR® for the treatment of neonatal seizures. Methods: This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days. Results: NOBELBAR® was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$. Conclusion: The study demonstrated that NOBELBAR® was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data. • Kawada 2011 at 206-07 The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an additional dose of 5 to 20 mg/kg intravenously over 5 to 10 minutes was allowed as long as the

'076 Patent Claim Limitation	Nobelbar												
	patient's plasma drug concentration was confirmed to be below 40 $\mu\text{g/mL}$. - Kawada 2011 at 209-210 The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of neonatal seizures at the dosages examined in the present trial. In addition, there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug. The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution. - Nobelbar Label [Composition and Characteristics] <table border="1"> <tr> <td>Brand name</td><td>Nobelbar 250 mg for injection</td></tr> <tr> <td>Ingredients and content</td><td>One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)</td></tr> <tr> <td>Additives</td><td>None</td></tr> <tr> <td>Formulation, color</td><td>White aggregate or powdered freeze-dried injection agent</td></tr> <tr> <td>pH</td><td>9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)</td></tr> <tr> <td>Ratio of osmotic pressure</td><td>2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)</td></tr> </table> - Nobelbar Label	Brand name	Nobelbar 250 mg for injection	Ingredients and content	One vial contains 274 mg of phenobarbital sodium (250 mg as phenobarbital)	Additives	None	Formulation, color	White aggregate or powdered freeze-dried injection agent	pH	9.2 ~ 10.2 (when dissolving 1 g in 10 mL of water)	Ratio of osmotic pressure	2.5 ~ 2.6 (when dissolving 1 g in 10 mL of water) (the ratio in relation to physiological saline)
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'076 Patent Claim Limitation	Nobelbar
	[Dosage and Administration] Neonatal seizures Initial dose: Perform intravenous administration of 20 mg/kg as phenobarbital. If it is not possible to control the convulsions, the dose may be adjusted for additional intravenous administration according to the patient's condition within a range that does not exceed the initial dose used. Maintenance treatment: Perform intravenous administration of 2.5 ~ 5 mg/kg as phenobarbital once a day. Status epilepticus Perform intravenous administration of 15 ~ 20 mg/kg as phenobarbital once a day. To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

R. Claim 18

'076 Patent Claim Limitation	Nobelbar
[18p] The pharmaceutical product of claim 8,	<i>See supra</i> Claim 8.

'076 Patent Claim Limitation	Nobelbar
[18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. • Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years. • PIF at 3

'076 Patent Claim Limitation	Nobelbar																
	III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
Type of test	Storage conditions	Storage method	Storage period														
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Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months														
Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months														

'076 Patent Claim Limitation	Nobelbar																							
	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
Type of test	Storage conditions	Storage method	Storage period																					
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'076 Patent Claim Limitation	Nobelbar																																																														
	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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Concentration of related substances (%)	0.09	0.19	0.49																																																												

'076 Patent Claim Limitation	Nobelbar
	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows 5-methyl-5-phenyl-barbituric acid Analogues that may be generated in the formulation manufacturing process are as follows 2-phenylbutyrylurea 2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

S. Claim 19

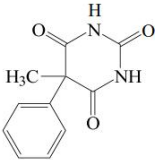
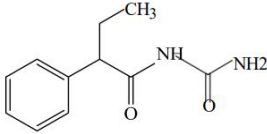
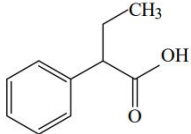
'076 Patent Claim Limitation	Nobelbar
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'076 Patent Claim Limitation	Nobelbar
[19p] The pharmaceutical product of claim 8,	<i>See supra</i> Claim 8.
[19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> Deliberation Results Report at 5 With regard to the stability of the drug substance manufactured at the actual production scale, a longterm storage test ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in a dark location, 60 months), an accelerated test ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, dark place, 6 months), and an intermediate test ($30 \pm 2^{\circ}\text{C}/65 \pm 5\% \text{ RH}$, dark place, 12 months) were performed in polyethylene bags and the bags were packed in a cardboard box¹. In these tests, property, solubility, pH, purity test (related substances), loss on drying, content were the test items, and in the acceleration test and intermediate test, confirmatory test (IR spectrum and melting point), purity test (related substances), and microbial limit were the test items. In these stability studies, no clear changes were observed in any of the measurements, and the storage method of the drug substance was set as “tight container, room temperature storage” and the re-test period of the drug substance was set at 5 years. Deliberation Results Report at 5 The stability of the formulation was evaluated by long-term storage tests (in paper boxes, $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$, in the dark, 36 months), accelerated tests (in paper boxes, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months), and caustic tests (temperature [in paper boxes, $50 \pm 2^{\circ}\text{C}/\text{normal}$ 3 months), and light (unpackaged, total illuminance of at least 1.2 million lux-hr + total near-ultraviolet radiation energy of at least 200 W-h/m²), and relative acceleration studies (paper boxed, upright/inverted, $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}/\text{dark}$, 3 months) were conducted on the formulations manufactured at production scale. In these tests, properties, identification test (qualitative reaction of IR spectrum, sodium salt), solubility, pH, purity test (related substances), water, loss of drying, foreign insoluble matter, insoluble particulate matter, and content were the test items, and endotoxin, product homogeneity (mass deviation) and sterility were the test items for long-term storage test and acceleration test. No clear changes were observed in any of the test items. Based on the above, the drug product is stored at room temperature and the primary packaging is sealed with glass vials, rubber stoppers and caps, and the expiry date of the drug product is set at 3 years.

'076 Patent Claim Limitation	Nobelbar																
	- PIF at 3 III-3. Stability of active ingredients under various conditions In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>Airtight container, dark area</td><td>60 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>Airtight container, dark area</td><td>6 months</td></tr><tr><td>Interim test</td><td>30±2°C/65±5%RH</td><td>Airtight container, dark area</td><td>12 months</td></tr></table> - PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months	Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months	Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months
Type of test	Storage conditions	Storage method	Storage period														
Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months														
Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months														
Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months														

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	IV-3. Methods of preparation of injectable drugs 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours). 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate). IV-4. Attention to dispersibility of suspensions and emulsions Not applicable IV-5. Stability of the formulation under various conditions The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial. <table><tr><th>Type of test</th><th>Storage conditions</th><th>Storage method</th><th>Storage period</th></tr><tr><td>Long-term storage test</td><td>25±2°C/60±5%RH</td><td>The sealed container was placed in a paper box.</td><td>36 months</td></tr><tr><td>Accelerated test</td><td>40±2°C/75±5%RH</td><td>The sealed container was placed in a paper box.</td><td>6 months</td></tr><tr><td>Relative comparison test</td><td>40±2°C/75±5%RH</td><td>Sealed container in upright and inverted position*1 and placed in a paper box.</td><td>3 months</td></tr><tr><td rowspan="2">Rigorous testing</td><td>50±2°C</td><td>The sealed container was placed in a paper box.</td><td>3 months</td></tr><tr><td>Light (1000±100 Lux at D65)</td><td>Sealed containers only. No packaging.</td><td>8 weeks</td></tr></table> *1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed. PIF at 5	Type of test	Storage conditions	Storage method	Storage period	Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months	Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months	Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months	Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks
Type of test	Storage conditions	Storage method	Storage period																					
Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months																					
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	IV-6. Stability after dissolution The product was dissolved in water for injection and physiological saline solution and examined for stability. Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.6</td><td>9.6</td><td>9.6</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.8</td><td>2.8</td><td>2.8</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>99.5</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light) <table><tr><th rowspan="2">Test item</th><th colspan="3">Storage period</th></tr><tr><th>At the start</th><th>6 hours</th><th>24 hours</th></tr><tr><td>Appearance</td><td>Clear and colorless</td><td>Clear and colorless</td><td>Clear and colorless</td></tr><tr><td>pH</td><td>9.5</td><td>9.5</td><td>9.5</td></tr><tr><td>Osmotic coefficient (compared to saline)</td><td>2.5</td><td>2.5</td><td>2.5</td></tr><tr><td>Foreign insoluble matter test</td><td>a</td><td>a</td><td>a</td></tr><tr><td>Content (% residual)</td><td>100.0</td><td>100.0</td><td>99.5</td></tr><tr><td>Concentration of related substances (%)</td><td>0.09</td><td>0.19</td><td>0.49</td></tr></table> a: Clear and free of clearly recognizable foreign insoluble matter PIF at 9	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.6	9.6	9.6	Osmotic coefficient (compared to saline)	2.8	2.8	2.8	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	99.5	99.5	Concentration of related substances (%)	0.09	0.19	0.49	Test item	Storage period			At the start	6 hours	24 hours	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	pH	9.5	9.5	9.5	Osmotic coefficient (compared to saline)	2.5	2.5	2.5	Foreign insoluble matter test	a	a	a	Content (% residual)	100.0	100.0	99.5	Concentration of related substances (%)	0.09	0.19	0.49
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	IV-9. Adulterants that may be contaminants Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows  5-methyl-5-phenyl-barbitaric acid Analogues that may be generated in the formulation manufacturing process are as follows  2-phenylbutyrylurea or  2-phenylbutyric acid • See generally Nobelbar Production; see, e.g., NOBEL-0027-0029; NOBEL-0037-0039; NOBEL-0081-0092; NOBEL-0109-0114; NOBEL-0134-0137; NOBEL-0151; NOBEL-0155-0161; NOBEL-0165-0167; NOBEL-0169-0175 To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun's Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the '076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person's understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

T. Claim 20

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[20p] The pharmaceutical product of claim 8,	<i>See supra</i> Claim 8.
[20a] wherein the composition is amorphous.	Nobelbar discloses and/or renders obvious this limitation based on at least the following citations. <i>See, e.g.:</i> • Deliberation Results Report at 1 The results of the review by the Pharmaceuticals and Medical Devices Agency concerning the following drug for which the application for approval was submitted are as follows. Record [Brand name] Nobelbar for intravenous injection 250 mg [Generic name] Phenobarbital sodium [Applicant name] Nobel Pharma K.K. [Application date] September 14, 2007 [Formulation/Strength] lyophilized drug product for intravenous infusion containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial [Category of application] Prescription drugs (3) Drugs with new route of administration [Special notes] Orphan drugs [Reviewing Department] Office of New Drug III • PIF at cover

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	Anticonvulsant Nobelbar® 250 mg for intravenous infusion (lyophilized phenobarbital sodium formulation) Nobelbar® 250 mg for injection Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)} Note 1) Caution: habit-forming Note 2) Caution: use only by prescription from a physician, etc. • PIF at 4 IV. Formulations IV-1. Dosage form (1) Dosage form classification, specifications and properties White mass or powder, lyophilized injection (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water) Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline) (3) Presence and type of special gases in the container of the injectable drug dry nitrogen IV-2. Composition of the preparation (1) Content of active ingredient (active constituent) 1 vial contains 274 mg of Phenobarbital Sodium (250 mg as phenobarbital) (2) additive not including

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	• Kawada 2009 at Title Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of “NOBELBAR®” and package insert information • Kawada 2009 at Abstract We would like to introduce this drug mainly to the parties involved in the release of NOBELBAR® 250mg for Injection (NOBELBAR® 250 mg for Injection, phenobarbital sodium lyophilized formulation) which was listed in the NHI price list as an anticonvulsant in December 2008. • Kawada 2009 at 9 The phenobarbital sodium lyophilized formulation NOBELBAR® 250mg for Injection that is released in this article is easily dissolved in water, and the ingredient changes over time when dissolved. • Kawada 2011 at 205 A lyophilized product of phenobarbital sodium entirely free of additives was used in this study. • Nobelbar Label Phenobarbital sodium freeze-dried preparation • <i>See generally</i> Nobelbar Production; <i>see, e.g.</i>, NOBEL-0203-0205; NOBEL-0203 (Fig. 5) To the extent Nobelbar does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of Nobelbar. Further, one of ordinary skill in the art would have been motivated to modify Nobelbar or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of Nobelbar.

