

Clinical Superiority Findings

In accordance with section 527(e)(2) of the FD&C Act (21 U.S.C. 360cc(e)(2)), FDA will publish a summary of the clinical superiority findings when a drug is eligible for orphan-drug exclusivity on the basis of a demonstration of clinical superiority. This page will only include the clinical superiority findings for those drugs approved on or after August 18, 2017, the date that the FDA Reauthorization Act of 2017 added section 527(e)(2) to the FD&C Act. "Clinical superiority," is used here only within the meaning of that term under FDA's orphan drug regulations at 21 CFR Part 316 and section 527(c) of the FD&C Act. For the definition of "clinically superior," for the purposes of determining eligibility for orphan-drug exclusivity when the same drug has been previously approved for the same use or indication, see 21 CFR 316.3(b)(3). For the definition of "same drug," see 21 CFR 316.3(b)(14).

The summary is organized by approval date.

2024

Flamel Ireland Limited dba Avadel Ireland for Lumryz (sodium oxybate)

Approval Date	10/16/2024
NDA/BLA	NDA 214755/S-006
Sponsor	Flamel Ireland Limited dba Avadel Ireland
Drug	Lumryz (sodium oxybate) for extended-release oral suspension
Orphan Designation	Treatment of narcolepsy
Approved Labeled Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Exclusivity Protected Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in pediatric patients 7 years of age and older with narcolepsy
Summary of Clinical Superiority Findings	The active moiety, oxybate, was previously approved as Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) for the treatment of cataplexy or EDS in pediatric patients 7 years of age and older with narcolepsy. The benefits of Lumryz's once-nightly dosing rise to the level of making a major contribution to patient care because Lumryz's dosing provides an opportunity to minimize sleep fragmentation and disruption of sleep architecture in a way that is not possible for a patient on a twice-nightly dosing regimen of oxybate. This is medically relevant because the goal for treating patients with sleep disorders is to restore a normal sleep pattern and a healthier sleep physiology. Aside from the medical benefits of not having to awaken to take a second dose, it is inherently more convenient, easier, and less burdensome for patients to forgo awakening to take a second dose on a nightly basis. Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment.

2023

Flamel Ireland Limited dba Avadel Ireland for Lumryz (sodium oxybate)

Approval Date	5/01/2023
NDA/BLA	NDA 214755
Sponsor	Flamel Ireland Limited dba Avadel Ireland
Drug	Lumryz (sodium oxybate) for extended-release oral suspension
Orphan Designation	Treatment of narcolepsy
Approved Labeled Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Exclusivity Protected Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Summary of Clinical Superiority Findings	The active moiety, oxybate, was previously approved as Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates) for the treatment of cataplexy or EDS in adults with narcolepsy. The benefits of Lumryz's once-nightly dosing rise to the level of making a major contribution to patient care because Lumryz's dosing provides for oxybate therapy that does not involve disrupting or fragmenting sleep, whereas Xyrem and Xywav necessitate a nocturnal awakening to take a second dose, which disrupts sleep architecture in patients with a known sleep disorder. Aside from the medical benefits of not having to awaken to take a second dose, it is inherently more convenient, easier, and less burdensome for patients to forgo awakening to take a second dose on a nightly basis. Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment.

2022**Mitsubishi Tanabe Pharma Corporation for Radicava ORS (edaravone) oral suspension**

Approval Date	5/12/2022
NDA/BLA	NDA 215446
Sponsor	Mitsubishi Tanabe Pharma Corporation
Drug	Radicava ORS (edaravone) oral suspension
Orphan Designation	Treatment of amyotrophic lateral sclerosis
Approved Labeled Indication	Treatment of amyotrophic lateral sclerosis (ALS)
Exclusivity Protected Indication	Treatment of amyotrophic lateral sclerosis (ALS)

Summary of Clinical Superiority Findings

The active moiety, edaravone, was previously approved as Radicava (edaravone) injection, for intravenous (IV) use for the treatment of amyotrophic lateral sclerosis (ALS). Radicava ORS makes a major contribution to patient care by providing an oral suspension route of administration that avoids the burdens of IV administration. IV administration requires the involvement of a healthcare professional to establish IV access and is inherently painful. Additionally, in some individuals IV access is difficult to obtain and is associated with potentially serious or life-threatening risks of infection. Radicava ORS is given orally or by feeding tube and can be self-administered.

Overall, Radicava's oral suspension route of administration advances the ease and comfort of administration without the complications and risks associated with IV administration. Importantly, this is in the context of a chronic and severe neurodegenerative disease that requires long-term treatment.

2020**Jazz Pharmaceuticals Ireland Limited for Xywav (calcium, magnesium, potassium, and sodium oxybates)**

Approval Date	7/21/2020
NDA/BLA	212690
Sponsor	Jazz Pharmaceuticals Ireland Limited
Drug	Xywav (calcium, magnesium, potassium, and sodium oxybates)
Orphan Designation	Treatment of narcolepsy
Approved Labeled Indication	Indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Exclusivity Protected Indication	Indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Summary of Clinical Superiority Findings	The active moiety, oxybate was previously approved as Xyrem (sodium oxybate) for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. Xywav (calcium, magnesium, potassium, and sodium oxybates) is clinically superior to Xyrem by means of greater safety because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem. The differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.

Chiesi USA, Inc. for Mycapssa

Approval Date	6/26/2020
NDA/BLA	NDA 208232

Sponsor	Chiesi USA, Inc.
Drug	Mycapssa (octreotide) delayed-release capsules, for oral use
Orphan Designation	The oral treatment of acromegaly
Approved Labeled Indication	Long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide
Exclusivity Protected Indication	Long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide
Summary of Clinical Superiority Findings	The active moiety, octreotide, was previously approved as Sandostatin (octreotide acetate) injection and Sandostatin LAR Depot (octreotide acetate) for injectable suspension, both for parenteral use in the treatment of acromegaly. Mycapssa makes a major contribution to patient care by providing an orally administered delayed-release capsule dosage form. Oral administration avoids the pain and risk of infection associated with parenteral administration. Additionally, Sandostatin LAR must be administered by a healthcare provider, while Mycapssa can be self-administered. Overall, Mycapssa improves patient comfort, reduces treatment burden, and advances the ease and comfort of drug administration. Importantly, this is in the context of a chronic and severe disease that may require long-term treatment.

2019**Neurelis Pharmaceuticals, Inc. for Valtoco (diazepam nasal spray)**

Approval Date	01/10/2020
NDA/BLA	NDA 211635
Sponsor	Neurelis Pharmaceuticals, Inc.
Drug	Valtoco (diazepam nasal spray)
Orphan Designation	Management of acute repetitive seizures
Approved Labeled Indication	Indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.
Exclusivity Protected Indication	Indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.
Summary of Clinical Superiority Findings	Diazepam was previously approved as a gel that is administered rectally for the same use as Valtoco (i.e., acute repetitive seizures). Valtoco's intranasal route of administration provides a major contribution to patient care over the rectal route of administration by providing a significantly improved ease of use. Rectal administration is inherently invasive for the patient and difficult to administer, whereas it is inherently more comfortable for the patient to receive the drug intranasally than rectally. In the context of when this drug is to be given, typically in the middle of a seizure event, it is inherently easier to administer the drug to a patient intranasally than rectally.

2018**CSL Behring for Hizentra**

Approval Date	03/15/2018
NDA/BLA	BLA 125350/S-641
Sponsor	CSL Behring
Drug	Hizentra (Immune Globulin Subcutaneous (Human), 20% Liquid)
Orphan Designation	Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP)
Approved Labeled Indication	Indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment
Summary of Clinical Superiority Findings	Immune Globulin (Human) was previously approved in an intravenous (IGIV) formulation for the same use as Hizentra (Immune Globulin Subcutaneous (Human), 20% Liquid). A substantial portion of CIDP patients receiving IGIV require a central venous access device (CVAD), which is associated with an increased risk of thromboembolic events and access-associated infections. These risks can be serious and/or life-threatening and the risks are long-term because CIDP is a chronic condition. Data demonstrated that patients treated with Hizentra subcutaneously had fewer of these adverse events than patients treated with IGIV via CVADs. Therefore, Hizentra provides greater safety than the previously approved IGIV formulation of immune globulin for CIDP as maintenance therapy for the purposes of orphan-drug exclusivity.

Astellas Pharma Global Development, Inc. for Prograf

Approval Date	05/24/2018
NDA/BLA	210115
Sponsor	Astellas Pharma Global Development, Inc.
Drug	Prograf (tacrolimus granules for oral suspension)
Orphan Designation	Prevention of rejection in kidney, liver, or heart transplant in pediatric patients
Approved Labeled Indication	The prophylaxis of organ rejection, in patients receiving allogeneic kidney transplant, liver transplants, and heart transplant, in combination with other immunosuppressants.

Summary of Clinical Superiority Findings

Tacrolimus has been previously approved for the same use in capsule and injection dosage forms. Pediatric patients who were unable to swallow capsules received extemporaneously compounded oral liquid tacrolimus preparations, which have not undergone product quality or clinical testing and have been associated with severe risks due to compounding errors. Because tacrolimus granules for oral suspension provides an age appropriate formulation for pediatric patients that avoids the severe risks associated with erroneously compounded tacrolimus, it provides greater safety than tacrolimus capsules for that population, for the purposes of orphan-drug exclusivity.

Tacrolimus injection contains castor oil as an inactive ingredient, which exposes patients to the serious risk of anaphylaxis. Because tacrolimus granules for oral suspension does not contain castor oil that exposes patients to the risk of anaphylaxis, it provides greater safety than tacrolimus injection for the purposes of orphan-drug exclusivity.

Novartis Pharmaceuticals Corporation for Signifor LAR

Approval Date	06/29/2018
NDA/BLA	203255/S-004
Sponsor	Novartis Pharmaceuticals Corporation
Drug	Signifor LAR (pasireotide)
Orphan Designation	Treatment of Cushing's disease
Approved Labeled Indication	Treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.
Summary of Clinical Superiority Findings	Signifor (pasireotide) was previously approved as an immediate release formulation for treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. There are no notable differences in the safety and efficacy profiles between the immediate release and long-acting formulations. The immediate release formulation requires twice daily subcutaneous injections. Signifor (pasireotide) long-acting release (LAR) is dosed once monthly by intramuscular (IM) injection. The dosing regimen of the LAR (once monthly) provides a major contribution to patient care over the dosing regimen of the immediate release (twice daily) due to the greatly reduced injections per month.

Leadiant Biosciences, Inc. for Revcovi (elapegademase-lvlr)

Approval Date	10/05/2018
NDA/BLA	BLA 761092

Sponsor	Leadiant Biosciences, Inc.
Drug	Revcovi (elapegademase-lvr)
Orphan Designation	Treatment of adenosine deaminase deficiency in patients with severe combined immunodeficiency
Approved Labeled Indication	Indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients
Exclusivity Protected Indication	Indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients
Summary of Clinical Superiority Findings	As defined in the orphan drug regulations, Revcovi (elapegademase-lvr) is the same drug as Adagen (pegademase bovine). Adagen was previously approved for the same indication as Revcovi. Compared to Adagen, Revcovi provides more stable adenosine deaminase (ADA) activity that is more consistently above the therapeutic threshold associated with clinical benefit. Also, at equivalent dose, patients converted from Adagen to Revcovi experience higher and more consistent ADA plasma activity. Furthermore, it has been determined that maintaining the plasma ADA activity above the therapeutic threshold is associated with long term survival in patients with ADA-SCID. Therefore, Revcovi is clinically superior to Adagen based on greater effectiveness.

Alexion Pharmaceuticals, Inc. for Ultomiris (ravulizumab-cwvz)

Approval Date	12/21/2018
NDA/BLA	BLA 761108
Sponsor	Alexion Pharmaceuticals, Inc.
Drug	Ultomiris (ravulizumab-cwvz)
Orphan Designation	Treatment of paroxysmal nocturnal hemoglobinuria
Approved Labeled Indication	Indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Exclusivity Protected Indication	Indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Summary of Clinical Superiority Findings	Under the definition of "same drug" in the orphan drug regulations, Ultomiris (ravulizumab-cwvz) is the same drug as Soliris (eculizumab), which was previously approved for treatment of PNH. The recommended maintenance dosing regimen for Ultomiris is every eight weeks, while the recommended maintenance dosing regimen for Soliris is every two weeks. Because each treatment session of the drug is associated with heavy treatment burdens, and because PNH is a chronic illness, the extended dosing interval of Ultomiris provides a major contribution to patient care over Soliris.

2017**Wyeth Pharmaceuticals, Inc., a Pfizer Company for Mylotarg**

Approval Date	09/01/2017
NDA/BLA	BLA 761060
Sponsor	Wyeth Pharmaceuticals, Inc., a Pfizer Company
Drug	Mylotarg (gemtuzumab ozogamicin)
Orphan Designation	Treatment of acute myeloid leukemia
Approved Labeled Indication	<ol style="list-style-type: none"> 1. Treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults, and 2. Treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older
Summary of Clinical Superiority Findings	<p>Mylotarg (gemtuzumab ozogamicin) received accelerated approval in 2000, under NDA 21174, for treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. Post-approval studies identified safety concerns including veno-occlusive disease, myelosuppression, infusion-related reactions, and early deaths. As a result, FDA requested that Wyeth voluntarily withdraw approval of Mylotarg from the market and Wyeth complied.</p> <p>The new approval for Mylotarg is for a lower dose and different schedule than the previous approval. In a cross-study analysis of clinical outcomes for patients with relapsed or refractory acute myeloid leukemia treated with single-agent Mylotarg, in comparison to the regimens using the previously approved regimen, patients treated with the new dosing regimen had less early mortality, less hepatotoxicity, less veno-occlusive disease, more rapid platelet recovery and less hemorrhage. Therefore, the sponsor has demonstrated that the newly approved dosing regimen is safer than the previously approved dosing regimen, and thus clinically superior for the purposes of orphan-drug exclusivity.</p>