CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210797Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210797
PDUFA Goal Date	October 8, 2019
OSE RCM #	2018-1327
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD, MPH
Review Completion Date	October 4, 2019
Subject	Evaluation of Need for a REMS
Established Name	Afamelanotide
Trade Name	Scenesse
Name of Applicant	Clinuvel Inc.
Therapeutic Class	Melanocortin-1 (MC1R) agonist
Formulation(s)	16 mg resorbable implant
Dosing Regimen	16 mg implanted subcutaneously every 60 days

Reference ID: 4501816

Table of Contents

Reference ID: 4501816

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Scenesse (afamelanotide) is necessary to ensure the benefits outweigh its risks. Clinuvel submitted a New Drug Application (NDA) 210797 for Scenesse with a proposed indication for the (b) (4) adult patients with erythropoietic protoporphyria (EPP). No serious risks have been identified with Scenesse. The Applicant submitted a non-REMS risk management plan that includes a (b) (4) Medication Guide (MG), and restrictive risk minimization measures.

DRISK has determined a REMS is not necessary to ensure the benefits of Scenesse outweigh its risks. No serious risks have been identified in clinical development program or via post-marketing data in Europe. As there are minimal numbers of patients with long term follow up in the US, a Post Marketing Requirement (PMR) to conduct a voluntary registry to obtain long-term safety information on afamelanotide will be required upon approval. Communicating information regarding theoretical risks and the continued need to employ sun protection measures will be done via the prescribing information.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Scenesse (afamelanotide) is necessary to ensure the benefits outweigh its risks. Clinuvel submitted a New Drug Application (NDA) 210797 for Scenesse with a proposed indication for the (b) (4) adult patients with erythropoietic protoporphyria (EPP). This application is under review in the Division of Dermatology and Dental Products (DDDP). The Applicant submitted a non-REMS risk management plan that includes a (b) (4) Medication Guide (MG) and restrictive risk minimization measures to ensure the benefits of Scenesse outweigh the Applicant's concerns regarding theoretical risks of melanoma, hypersensitivity reactions, implantation administration errors, and off-label use for aesthetic tanning.[1,2]

2 Background

2.1 Product Information

Scenesse (afamelanotide), a new molecular entity (NME)[a], is a melanocortin-1 receptor (MC1R) agonist and structural analog of α-melanocyte stimulating hormone (α-MSH). The drug's mechanism of action is to promote eumelanin production via stimulation of MC1R, leading to increased sunlight tolerance via absorption of sunlight, scattering of sunlight, and antioxidant activity.[3] The Applicant proposed an indication (b) (4) in adult patients with erythropoietic protoporphyria (EPP). Scenesse is supplied as a 16 mg controlled-release implant, with the drug dispersed in a bioresorbable polymer, to be administered subcutaneously every 60 days in the suprailiac area and is intended for

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

lifelong treatment.[b] Scenesse was given an orphan drug designation on July 17, 2008, and a fast track designation on June 29, 2016.[4,5] Scenesse was granted authorization by the European Medicines Agency (EMA) on December 22, 2014, under exceptional circumstances, with commercial marketing commencing on June 22, 2016.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 201797 relevant to this review:

- 7/17/2008: Orphan designation for afamelanotide granted.
- 6/29/2016: Fast track designation for afamelanotide granted.
- 11/7/2016: Applicant informed at pre-NDA meeting that a REMS for Scenesse was likely not needed.[6]
- 11/8/2018: NDA 210797 rolling review submission for the (b) (4) adult patients with EPP completed.
- 3/22/2019: A Mid-Cycle Teleconference was held with the Applicant, in which they were informed that the proposed risk management plan for afamelanotide was still under review.[7]
- 5/10/2019: The Applicant submitted an amendment to the NDA detailing information regarding the administration device for afamelanotide implant.[8]
- 5/31/2019: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended by 3 months.[9]

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION[10]

Erythropoietic protoporphyria (EPP) is a serious genetic disorder characterized by deficient activity of the enzyme ferrochelatase, which converts protoporphyrin IX (PP IX) to heme. Patients with EPP have elevated levels of PP IX in the skin, blood, and liver. On light exposure, PP IX in the dermis is excited and leads to a phototoxic reaction. The excess energy dissipates to neighboring molecules directly or via reactive oxygen species, reported by patients to cause an immediate pain and burning sensation (not relieved by pain medications) and may progress to skin edema and erythema. The reaction persists for several days and over time, due to repeated phototoxic reactions, the skin may become thickened, usually without scarring or dyspigmentation.[c] In some patients, the disease can lead to gallbladder and liver complications (cholestasis, cholelithiasis, cholecystitis, chronic liver failure), including acute liver failure requiring liver transplantation in up to 5% of EPP patients. In the United States, the prevalence of

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

EPP is estimated to be 1/75,000, with 225 patients reported registered with the American Porphyria Foundation.[d] Patients with EPP are conditioned to practice life-long sun avoidance that restricts their activities of daily living, employing full sun protection when outdoors and choosing to often travel at night.

3.2 Description of Current Treatment Options[11]

Currently, there are no approved products for the treatment of EPP. Current treatment is focused on strict sun avoidance (sun protective clothing, sunscreen). Oral beta-carotene and phototherapy have been used with little success in EPP patients.[12] Once the phototoxic reaction has occurred, analgesics can used for pain relief, but may not be effective in all cases.

4 Benefit Assessment

The Applicant submitted three studies in support of the proposed indication, studies CUV029 (Phase 3), CUV030 (Phase 2), and CUV039 (Phase 3).[13] Due to issues with data integrity in studies CUV029 and CUV030 (which the EMA deemed non-GCP compliant in their review), only study CUV039 is considered as a pivotal efficacy study and the other two are supportive in nature. All three studies were conducted as multi-center, placebo-controlled trials, studying Scenesse 16 mg implanted subcutaneously every 2 months in a total of 244 adult patients with EPP.

Study CUV039 provided evidence of the effectiveness of afamelanotide to increase the duration of pain-free sun exposure time in adults with EPP who do not have significant hepatic involvement. The trial's primary endpoint was the change from baseline to Month 6 compared to placebo of the duration of direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced.

Studies CUV029 and CUV030 provide supportive evidence of the conclusions of Study CUV039. Study CUV030 evaluated the primary endpoint of the number of hours of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced. Study CUV029 evaluated a modified primary endpoint of time spent in direct sunlight between 10:00 and 15:00 and 10:00 and 20:00 hours. Table 1 shows the trial design of the three phase 3 studies submitted:

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Reference ID: 4501816

Table 1 – Trial Design for Phase 3 Studies for afamelanotide

Trial Identity	Trial Design	Regimen/ schedule/ route	Primary Efficacy Endpoints	Treatment Duration/ Follow Up	# of patients enrolled
Efficacy and safety					
CUV039	Phase 3, multicenter (MC), placebo-controlled (PC) trial	Afamelanotide (afa) 16 mg implant subcutaneously (SC) every 2 months (Q2M) (Day 0, 60, and 120)	Duration of direct sunlight exposure between 10:00 and 18:00 hours on days when no pain was experienced	3 implants/6 months with safety follow-up 1 year	93 Afa: 48 Plc: 45
CUV030	Phase 3, MC, PC trial	Afa 16 mg implant SC Q2M (Day 0, 60, and 120)	Number of hours of direct sunlight exposure between 10:00 and 15:00 hours on days when no pain was experienced (pain score 0).	3 implants/6 months	77 Afa: 39 Plc: 38
CUV029	Phase 3, MC, PC trial	Afa 16 mg implant SC Q2M (Day 0, 60, 120, 180, and 240)	Time spent in direct sunlight between 10:00 and 15:00 and 10:00 and 20:00 hours	5 implants/9 months	74 Afa: 38 Plc: 36

Several factors potentially confound the results of the efficacy studies. At baseline, subjects had varying baseline levels of light tolerance, from less than a minute to several hours in a day. Additionally, the mechanism of action of afamelanotide leads to functional unblinding of subjects – patients receiving study drug would develop a tan noted within weeks after the first implant administration. Treatment with afamelanotide allows an increase in the amount of time spent in the sun without triggering a phototoxic reaction. This in turn allows patients the ability to have more normal daily routines (e.g., walk from car to grocery store without need for full sun protective clothing), and may skew the results based on their altered activity patterns.

Despite potential confounding, Afamelanotide demonstrated superiority to placebo ($p < 0.044$) on the primary endpoint in Study CUV039 and is supported by the results of Studies CUV029 and CUV030, which trended in the same direction despite issues with data integrity. The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on the improvement in hours of direct sunlight exposure in Study CUV039.[14,e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

The safety population for this application is based on the three phase 3 studies included in the benefit assessment for afamelanotide.[15] Adverse reactions that occurred in more than 2% of subjects are listed in Table 2 below:

Table 2 - Proportion of Subjects with Adverse Reactions Occurring in More Than 2% of Subjects (Studies CUV029, CUV030, and CUV039)

Adverse Reaction	SCENESSE n (%) N = 125	Vehicle n (%) N = 119
Implant site reaction[1]	25 (20%)	12 (10%)
Nausea	24 (19%)	17 (14%)
Oropharyngeal pain	9 (7%)	6 (5%)
Cough	8 (6%)	4 (3%)
Fatigue	7 (6%)	3 (3%)
Skin hyperpigmentation[2]	5 (4%)	0 (0%)
Melanocytic nevus	5 (4%)	2 (2%)
Respiratory tract infection	5 (4%)	3 (3%)
Porphyria non-acute	2 (2%)	0 (0%)
Skin irritation	2 (2%)	0 (0%)

[1]: Implant site reaction includes: implant site bruising, discoloration, erythema, hemorrhage, hypertrophy, irritation, nodule, pain, pruritus, swelling; injection site bruising, erythema, and administration site reaction.
[2]: Skin hyperpigmentation includes skin hyperpigmentation, pigmentation lip (subject also had skin hyperpigmentation), and pigmentation disorder.

Treatment with afamelanotide implant was not associated with an increased risk of mortality or serious adverse events. In the safety population, there were no deaths and serious adverse events (SAEs) occurred in 4% of subjects in the afamelanotide group versus 3% of subjects in the vehicle group. None of the SAEs were considered to be drug-related. The most common adverse reactions include implant site reactions (afamelanotide 20% versus vehicle 10%) and skin hyperpigmentation (afamelanotide 4% versus vehicle 3%). No adverse events related to study drug led to study discontinuation.

In the safety population (Studies CUV029, CUV030, and CUV039), five subjects who received afamelanotide experienced 6 serious adverse events (SAEs) and 3 subjects who received vehicle experienced 4 SAEs. All subjects who experienced SAEs had resolution of the SAE without sequelae. All SAEs reported in subjects receiving afamelanotide were considered by the clinical reviewer as not related or unlikely to be related to study drug. The table below summarizes the reported SAEs:

Table 3 - 1Treatment emergent serious adverse events in the safety population (Studies CUV029, CUV030, and CUV039)

	Preferred Term	Afamelanotide 16 mg n (%)	Vehicle, n (%)
Subjects reporting SAEs, n (%)		**5 (4%)**	**3 (3%)**
Number of SAEs		**6**	**4**
	Abdominal pain	2 (2%)	
	Hospitalization	1 (1%)	
	Intervertebral disc protrusion	1 (1%)	
	Melanocytic nevus	1 (1%)	
	Rectal hemorrhage	1 (1%)	
	Malignant melanoma in situ		1 (1%)
	Dizziness		1 (1%)
	Heart rate decreased		1 (1%)
	Pulmonary embolism		1 (1%)

In addition to the clinical development program, the Applicant submitted safety data obtained from required European Medicines Agency (EMA) post marketing safety studies (PASS) to support the safety information. EMA post marketing data included patients treated with afamelanotide implant through Compassionate Use and Expanded Access programs. The EMA post marketing exposure data included patients with EPP with up to 10 years of afamelanotide exposure. Per the Applicant, 246 patients with EPP have been treated under the PASS protocols as of March 31, 2018. The Applicant also reports 323 patients treated with afamelanotide under Compassionate Use and Special Access programs. Post marketing data submitted from the European markets did not reveal new safety signals.

Five deaths occurred during the post marketing period in Europe in EPP patients under compassionate or expanded access programs, however none of the deaths are attributed to afamelanotide (cardiac arrest secondary to arrhythmia, metastatic breast cancer, metastatic squamous cell carcinoma, brain tumor, sepsis with multiorgan failure).[11]

5.1 ADVERSE EVENTS OF SPECIAL INTEREST

5.1.1 Melanocytic Proliferation and Melanogenesis

The phase 3 clinical trials were designed to include dermatologic examinations to screen for cutaneous malignancies (melanoma and non-melanoma), to evaluate whether afamelanotide increased the risk of these malignancies. In the safety population, 1 subject who received afamelanotide experienced an adverse reaction related to a melanocytic lesion. The subject in question was a 56-year-old male, with a

history of over "30 nevi, all less than 6mm but some with fried egg or slightly irregular in border consistent with atypical nevi."[16] The subject had two nevi removed which were classified as "compound nevus with atypical dysplasia" and "compound nevus," of unknown severity, and unlikely related to study drug. The clinical reviewer determined that the subject appears to have a phenotype of multiple atypical nevus, and it is unclear if afamelanotide contributed to the dysplasia in the subject's melanocytic lesions. The clinical reviewer recommends the Prescribing Information include skin monitoring in Section 5 Warnings and Precautions.

Patients with EPP are not at an increased risk of skin cancer, including melanoma, at baseline.[17,f] Standard of care for EPP patients include bi-annual comprehensive visits to a team of specialists, including dermatologists who perform skin monitoring.

6 Expected Postmarket Use

Afamelanotide is expected to be administered in-office by specialists or primary care physicians who regularly treat EPP patients. The administration technique required to implant afamelanotide falls under the scope of general medical practice, as the administration is completed by using an approved cannula and needle. In the clinical development program, a diverse group of practitioners administered the drug, and it is likely that similar diversity will exist in the post-market setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant has proposed a non-REMS risk management plan that contains restrictive risk minimization measures.[18] This proposed plan is based on the risk minimization plan included in the authorization granted by the European Medicines Agency (EMA).[19] The plan is designed to mitigate the theoretical risks of administration errors, administration site reactions, changes of pigmentary expression, and off-label use, as well as to provide a mechanism to further characterize the long-term safety of Scenesse. The Applicant has proposed the following in their risk management plan:

- Prescriber training and certification on the implant technique
- 30-minute observation period post-implantation
- Full body skin exams every 6 months
- Restricted distribution to porphyria treatment centers
- Global disease registry

In addition to the above, (b) (4) a Medication Guide, and routine pharmacovigilance activities.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of afamelanotide on the basis of the efficacy and safety information currently available.[10]

Erythropoietic protoporphyria (EPP) is an uncommon, lifelong genetic disorder resulting in pain with light exposure and leads to life-long sun avoidance that significantly impacts quality of life. There are currently no FDA-approved products for EPP and current management includes daily strict photoprotection. The afamelanotide implant provides an effective and safe treatment option for patients with EPP without significant hepatic involvement.

The Applicant proposed a non-REMS risk management plan to mitigate theoretical risks. This risk management plan was based on the currently approved risk minimization plan put in place by the EMA. DRISK consulted EMA as to rationale for the restrictive plan implemented upon authorization of Scenesse in Europe. The EMA emphasized that due to limited safety information at the time of approval (as it was authorized through their exceptional circumstances[g] pathway) and the unknown long term safety profile of the drug, they implemented a plan that would ensure any theoretical risks were mitigated, long term safety data could be collected, and off-label use could be prevented within the closed medical systems of the European market.[20] In context of the lack of risks seen with in the clinical development program in the United States, as well as post marketing safety data collected by the EMA, the risk management plan proposed for the NDA is not necessary as no serious risks have been observed with use of the drug.

Healthcare providers can implant the drug using the appropriate device approved in the proposed prescribing information (PI) and by following the implantation instructions in the PI. The subcutaneous implantation procedure is within the scope of general clinical practice for physicians and the implant does not need to be removed. There is no evidence of serious hypersensitivity or anaphylactic reactions in development or post-marketing that would require special recommendations for additional monitoring.

Patients with EPP are not at an increased risk of skin cancer, including melanoma, at baseline. There were no reports of skin cancer during the clinical trials or in EMA post marketing monitoring, which includes up to 10 years of use in subjects via compassionate use programs. There is no evidence of increased melanoma in patients, and EPP patients are screened regularly by a dermatologist as a standard of care for EPP patients.

The Sponsor will be expanding the voluntary registry to the United States as a post-marketing requirement (PMR), to further characterize the long-term safety of afamelanotide. Under the PMR, patients will be followed for a minimum of eight years from initiation of treatment with afamelanotide. Safety information collection will include the following: changes in pigmentary expressions, skin cancers

[g] A type of marketing authorization granted by the EMA to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.

(melanomas and non-melanomas), pregnancy outcomes (including major birth defects and other adverse pregnancy outcomes such as spontaneous abortions, stillbirths, preterm deliveries, and small for gestational age), exposure during lactation and adverse reactions in breastfed infants, (b) (4) and, implant and administration errors.

As there are no serious risks to mitigate associated with Scenesse, professional and patient labeling, routine pharmacovigilance, and the PMR registry are adequate to communicate theoretical risk and obtain further long-term safety data about the drug; a Risk Evaluation and Mitigation Strategy (REMS) is not necessary.[h]

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. There are no serious risks associated with afamelanotide treatment, and healthcare providers who treat EPP are familiar with the importance of regular patient monitoring.

Should the Division of Dermatology and Dental Products have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

[1] Clinuvel. Proposed Prescribing Information for Scenesse, November 8, 2018.

[2] Clinuvel. Risk Management Plan for Scenesse, November 8, 2018.

[3] Clinuvel. Clinical Overview for Scenesse, November 8, 2018.

[4] U.S. Food and Drug Administration. Orphan Drug Designation for afamelanotide, July 17, 2008.

[5] Division of Dermatology and Dental Products. Grant Fast Track Designation Letter for IND 103131, Scenesse (afamelanotide), June 28, 2016.

[6] Division of Dermatology and Dental Products. Pre-NDA Meeting Minutes for IND 103131, Scenesse (afamelanotide), November 22, 2016.

[7] Division of Dermatology and Dental Products. Mid-Cycle Communication for NDA 210797, Scenesse (afamelanotide), April 8, 2019.

[8] Clinuvel. Major Amendment to NDA 210797, Scenesse (afamelanotide). eCTD Sequence 0039, May 10, 2019.

[h] At a REMS Oversight Committee (ROC)[h] meeting held on May 1, 2019, the ROC also concurred with this conclusion.

Reference ID: 4501816

[9] Division of Dermatology and Dental Products. Major Amendment Extension Letter for NDA 210797, Scenesse (afamelanotide), May 31, 2019.

[10] Draft unireview Scenesse (afamelanotide), NDA 210797, September 2, 2019.

[11] Clinuvel. Clinical Overview for Scenesse, November 8, 2018.

[12] Minder EI, et al. A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. Cell Mol Biol (Noisy-le-grand) 2009; 55:84.

[13] Clinuvel. Summary of Clinical Efficacy for Scenesse, November 8, 2018.

[14] Division of Dermatology and Dental Products. Draft Unireview for Scenesse (afamelanotide), NDA 210797, September 3, 2019.

[15] Clinuvel. Summary of Clinical Safety for Scenesse, November 8, 2018.

[16] Clinuvel. Summary of Clinical Safety for Scenesse, November 8, 2018.

[17] REMS Oversight Committee (ROC) Presentation, May 1, 2019.

[18] Clinuvel. Risk Management Plan for Scenesse, November 8, 2018.

[19] Clinuvel. EU Risk Management Plan for Scenesse, Month XX, 20XX.

[20] European Medicines Agency. Response to FDA Inquiry about Risk Management Rationale for NDA 210797, Scenesse (afamelanotide). February 19, 2019.

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/s/

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