

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761090Orig1s000

**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	BLA
Application Number	761090
PDUFA Goal Date	August 24, 2018
OSE RCM #	2017-2628
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	August 11, 2018
Subject	Evaluation of need for a REMS
Established Name	Lanadelumab
Trade Name	Takhzyro™
Name of Applicant	Dyax Corp.
Therapeutic Class	Monoclonal antibody
Formulation(s)	150 mg/mL solution
Dosing Regimen	300 mg administered by subcutaneous injection every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Takhzyro™ (lanadelumab) is necessary to ensure the benefits of the product outweigh its risks. Dyax Corp. (Dyax) submitted Part 4 of a Rolling Biologics License Application (BLA 761090) on December 26, 2017, for lanadelumab with the proposed indication of prophylaxis to prevent attacks [REDACTED] ^{(b) (4)} of hereditary angioedema in patients 12 years of age and older. The most important safety concern associated with the administration of lanadelumab is hypersensitivity. Elevated liver function tests emerged as a potential safety signal; however, increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and in some cases confounded by underlying co-morbidities. The Applicant did not submit a REMS or risk management plan with the application.

DRISK and the Division of Pulmonary, Allergy, and Rheumatology Products agree that a REMS is not necessary to ensure the benefits of lanadelumab outweigh the risks. Hereditary angioedema (HAE) is a rare and serious disease characterized by recurrent episodes of angioedema attacks that range in severity from cutaneous swelling to life-threatening laryngeal edema that may lead to fatal asphyxiation. There are three products approved in the U.S. for the prevention of HAE attacks, including two plasma-derived protein concentrates and the androgen therapy danazol. Lanadelumab is associated with fewer serious risks than the approved products and offers an improved dosing regimen compared with the plasma-derived protein products. None of the approved products has required a REMS or other risk management program. The efficacy of lanadelumab has been established based on the significant reduction in the mean HAE attack rate per month compared with placebo, as well as significant reductions in the mean monthly attack rates for all secondary endpoints compared to placebo. Based on the safety profile and efficacy demonstrated in the clinical trials, risk mitigation beyond labeling is not required.

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 Takhzyro™ (lanadelumab) is necessary to ensure the benefits of the product outweigh its risks. Dyax submitted Part 4 of a Rolling Biologics License Application (BLA 761090) on December 26, 2017, for lanadelumab with the proposed indication of prophylaxis to prevent attacks [REDACTED] ^{(b) (4)} of hereditary angioedema in patients 12 years of age and older. This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The Applicant did not submit a REMS or risk management plan with the application.

2 Background

2.1 PRODUCT INFORMATION

Takhzyro™ (lanadelumab), a new molecular entity^a, is a humanized monoclonal antibody that binds and inhibits soluble and membrane-bound active plasma kallikrein. Inhibition of kallikrein prevents cleavage

^a FDAAA factor (F): Whether the drug is a new molecular entity.

of high molecular weight kininogen, which results in subsequent release of bradykinin. Excessive production of bradykinin, which is a potent vasodilatory mediator, leads to capillary plasma leakage and angioedema. Lanadelumab is supplied as a 150 mg/mL solution in single-use vials that require refrigeration. The Applicant's proposed dose regimen is 300 mg administered by subcutaneous injection every two weeks as chronic therapy; a dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.^b Lanadelumab received orphan product designation on November 26, 2013 for the treatment of hereditary angioedema and breakthrough therapy designation on July 2, 2015 for the prevention of angioedema attacks in patients with hereditary angioedema. Lanadelumab is not currently approved in any other jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761090 relevant to this review:

- 11/26/2013: Orphan product designation granted for the treatment of hereditary angioedema.
- 7/2/2015: Breakthrough Therapy designation granted for the prevention of angioedema attacks in patients with hereditary angioedema (IND 116647).
- 10/31/2017: BLA 761090 Rolling Submission Part 1, Nonclinical received by the Agency.
- 11/17/2017: BLA 761090 Rolling Submission Part 2, CMC Part 1 received by the Agency.
- 12/4/2017: BLA 761090 Rolling Submission Part 3, CMC Part 2 received by the Agency.
- 12/26/2017: BLA 761090 Rolling Submission Part 4, Clinical received by the Agency. This submission started the PDUFA review clock.
- 4/10/2018: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency stated there have been no safety issues identified to date that would require a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hereditary angioedema (HAE) is a rare, serious, autosomal dominant disease that results from excessive production of bradykinin. The disease is characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Attacks are self-limited, lasting two to four days, and range in severity from cutaneous swelling to life-threatening laryngeal edema that may cause fatal asphyxiation.^c Gastrointestinal attacks present as varying degrees of colic, nausea, vomiting, and diarrhea that result from bowel wall edema. For the majority of patients, the disease first presents in childhood or adolescence and is generally a lifelong condition. HAE is a rare disease with an estimated prevalence range of 1:10,000 to 1:150,000 persons.^{1,d}

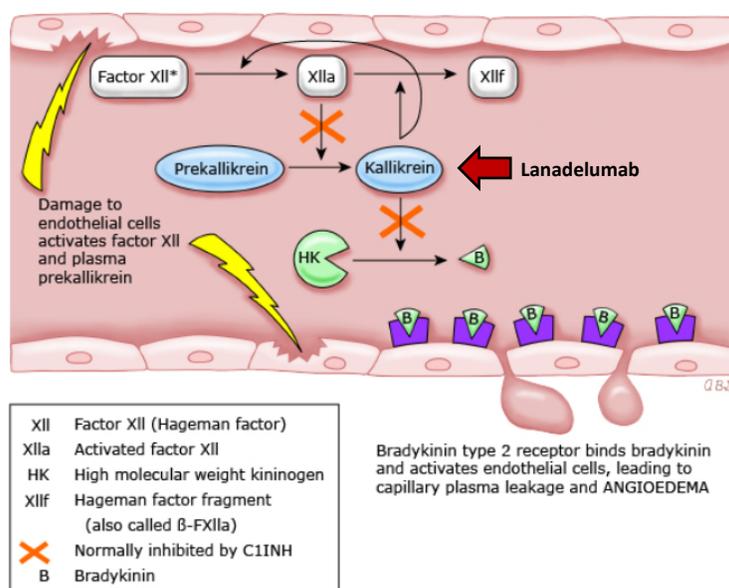
^b FDAAA factor (D): The expected or actual duration of treatment with the drug.

^c FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

^d FDAAA factor (A): The estimated size of the population likely to use the drug involved.

The pathophysiology of HAE is related to a deficiency or dysfunction of the serine protease C1 inhibitor (C1INH), which regulates kallikrein and other factors and enzymes in the complement pathways. Type I HAE is characterized by reduced secretion of C1INH whereas Type II HAE results from the presence of a dysfunctional C1INH protein. C1INH normally keeps bradykinin production in check through the inhibition of kallikrein activity on high molecular weight kininogen (HK) and the inhibition of activated Factor XII, which converts prekallikrein to kallikrein. Therefore, a deficiency or dysfunction of C1INH results in a loss of regulatory inhibition on kallikrein, resulting in elevated levels of bradykinin.² As mentioned in Section 2.1 of this review, lanadelumab binds and inhibits kallikrein. Inhibition of kallikrein prevents cleavage of HK and subsequent release of bradykinin. See Figure 1 below for a diagram of the pathways involved.

Figure 1. Pathways involved in kinin-mediated angioedema



C1INH: C1 inhibitor

Figure adapted from: Cicardi M, Zuraw B. Hereditary angioedema: Pathogenesis and diagnosis. In:UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham, MA 2018

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are three treatments currently approved for the prevention of HAE attacks (see Table 1 below). These include plasma-derived C1INH, administered either by intravenous infusion (Cinryze) or subcutaneous injection (Haegarda), and the oral androgen danazol. Treatment with Cinryze must be administered every 3 or 4 days and may necessitate placement of an indwelling venous catheter, which in itself carries risks of thrombotic events and infection. Subcutaneous injection of Haegarda has the advantage of allowing self-administration by the patient, but it too requires dosing every 3 or 4 days. C1INH concentrates are associated with hypersensitivity reactions and thromboembolic events, and a theoretical risk of disease transmission. Danazol is associated with multiple serious risks; its androgenic effects may not be tolerated in female patients and the drug should not be used in prepubertal children. None of these products has required a REMS to manage their serious risks. In addition to the approved

treatments, other anabolic androgens and antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid are used off-label for the prophylaxis of HAE attacks.³

A number of products are approved for the acute treatment of HAE including plasma-derived C1INH (Cinryze, Berinert) and recombinant C1INH (Ruconest); the bradykinin B2 receptor antagonist icatibant (Firazyr); and the kallikrein inhibitor ecallantide (Kalbitor). Due to the risk of anaphylaxis, Kalbitor was approved with a communication plan REMS on December 1, 2009; the REMS was eliminated April 10, 2013 because the communication plan was complete and it was determined that the REMS met its goals.

Table 1. Treatments approved for prevention of angioedema attacks in patients with HAE

Product Name (Trade Name) Year of Approval	Dosage and Administration	Warnings and Precautions	Efficacy
C1 esterase inhibitor [human] (Cinryze) 2008	1,000 units IV every 3 or 4 days	Hypersensitivity reactions Thromboembolic events Transmissible infections agents	Mean number HAE attacks over 12 weeks: Cinryze 6.1 vs. placebo 12.7
C1 esterase inhibitor [human] (Haegarda) 2017	60 units/kg SC every 3 or 4 days	Hypersensitivity reactions Thromboembolic events Transmissible infections agents	Mean number HAE attacks per month: Haegarda 0.5 vs. placebo 4.0
Danazol c. 1981	Up to 600 mg oral daily. Dose adjustment based on response.	Contraindicated in pregnancy Androgenizing effects Thromboembolic events Hepatotoxicity Pseudotumor cerebri Dyslipidemia Fluid retention	Not presented in the label. A summary review identified multiple literature reports that describe reductions in the severity and frequency of HAE attacks and improvement of clinical symptoms. ⁴

4 Benefit Assessment

The clinical trial (Study DX-2930-03 [NCT 02586805]) supporting the application is a Phase 3, randomized, double-blind, placebo-controlled, parallel group study in 125 adolescent and adult patients 12 years of age and older with Type I/II HAE. Patients were randomized to one of four groups and received six months of treatment with lanadelumab 150 mg every 4 weeks (n=28); 300 mg every four weeks (n=29); 300 mg every two weeks (n=27); or placebo every two weeks (n=41). Patients who completed the treatment period could rollover into an open label extension (Study DX-2930-04 [NCT02741596]) and receive lanadelumab for an additional 30 months (the extension study also enrolled patients who did not participate in Study-03). The primary efficacy endpoint of Study-03 was the mean HAE attack rate during the treatment period. Multiple secondary endpoints were also evaluated, including the mean number of HAE attacks requiring acute treatment and the mean number of moderate or severe HAE attacks during the treatment period, among other endpoints.⁵

For the primary endpoint in Study-03, the least squares mean HAE attack rate per month over six months of lanadelumab treatment was 0.48 in the 150 mg every 4 weeks group; 0.52 in the 300 mg every 4 weeks group; and 0.26 in the 300 mg every 2 weeks group; compared with 1.97 in the placebo group.

These results represent reductions in the mean HAE attack rate compared to placebo of 76%, 73%, and 87% (adjusted $p < 0.001$), respectively. All 3 lanadelumab dosing regimens also showed a significant reduction in the least squares mean monthly attack rate for all rank ordered secondary endpoints, compared to placebo (adjusted $p < 0.001$ for all). The clinical review team concluded that substantial evidence of efficacy has been established for the use of lanadelumab to prevent attacks of hereditary angioedema in patients with Type I or II HAE based on the primary endpoint of monthly attack rate and multiple supportive endpoints.^{e,6}

5 Risk Assessment & Safe-Use Conditions

The safety population is comprised of 257 patients who were exposed to lanadelumab during the clinical development program. This number includes 233 patients with HAE and 24 healthy subjects.

5.1 SERIOUS ADVERSE EVENTS^{f,g,h}

No deaths were reported in any of the lanadelumab clinical studies. In the placebo-controlled Phase 3 study, serious adverse events (SAEs) during the treatment period were reported in 4 patients in the lanadelumab arms and no patients in the placebo arm. The SAEs associated with lanadelumab included catheter site infection, pyelonephritis, meniscus injury, and bipolar disorder. In the open-label extension (OLE) study, a total of 8 patients experienced a total of 11 SAEs; the events included two reports of spinal stenosis; systemic lupus erythematosus; lymphoedema; gastroenteritis; fibrosarcoma, incision site inflammation, and wound dehiscence in a single patient; anal fissure; and accidental exposure to caustic agent and gastrointestinal hemorrhage in a single patient. Two additional SAEs from the OLE, including suicidal ideation and hypochromic anemia, were reported in the 120-Day Safety Update.^{7,8} The clinical reviewer noted the SAEs in Study-03 and the OLE study were primarily single events and appear to be unrelated to lanadelumab treatment.^{6,i}

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Hypersensitivity Reactions

There were five reports of the MedDRA preferred term hypersensitivity in four lanadelumab-treated patients, with all events considered related to treatment by the investigators. There were no such reports in the placebo group. The reported symptoms associated with lanadelumab hypersensitivity included itchiness, tingling, and discomfort of tongue; rash at injection site and swelling of eyes; itching,

^e FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

^g 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.

^h Serious adverse events that involved HAE attacks are excluded from the report counts.

ⁱ Email communication, Stacy Chin, Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products, June 15, 2018.

hives, headache, and burning sensation; and edema, wheals, and joint pain. The clinical reviewer noted there were no events of anaphylaxis in the clinical development program.

5.2.2 Elevated Liver Function Tests

During the placebo-controlled treatment period, 3 of 84 (3.6%) lanadelumab-treated patients experienced elevations over baseline in ALT value to 3-5x the upper limit of normal (ULN) (2 patients) or >5x ULN (1 patient); 2 of 84 (2.4%) patients had an increase in AST value to 3-5x ULN or >5x ULN. There were no transaminase elevations to these levels in the placebo arm. No patient experienced an increase in total bilirubin \geq 2x ULN during the treatment period.

In the OLE study (including data from the 120-Day safety update) six patients experienced increases in ALT (> 3x ULN) above baseline and six patients experienced increases in AST (> 3x ULN) above baseline. One case reported an increase in total bilirubin \geq 2 x ULN. There were no cases that met the criteria for Hy's law.

The clinical reviewer noted that the increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and in some cases confounded by underlying co-morbidities.

6 Expected Postmarket Use

Lanadelumab is likely to be prescribed by allergists and clinical immunologists who have experience in treating HAE. It is expected that the drug will primarily be used in the outpatient setting as chronic therapy and will be administered subcutaneously by self-injection or injection by a caregiver. Healthcare professionals will need to provide proper training to patients and/or caregivers on the administration of lanadelumab according to the Instructions for Use included in the product labeling.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS or risk management plan with the application.

8 Discussion of Need for a REMS

Hereditary angioedema is a rare, serious, autosomal dominant disease that results from excessive production of bradykinin. The disease is characterized by recurrent episodes of angioedema that most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Attacks are self-limited but range in severity from cutaneous swelling to life-threatening laryngeal edema that may cause fatal asphyxiation.

Three products are approved in the U.S. for the prevention of HAE attacks, which include two plasma-derived C1INH concentrates and the androgen therapy danazol. In contrast with the C1INH products, lanadelumab is not associated with thromboembolic adverse events or a potential risk of infectious disease transmission. The lanadelumab biweekly dosing schedule also offers a clinical advantage compared to the dosing requirements of the C1INH products, which require administration every 3-4

days. Androgen therapy is associated with multiple serious risks and cannot be used in prepubertal children or during pregnancy.

The lanadelumab clinical program showed that substantial evidence of efficacy has been established based on the significant reduction in the mean HAE attack rate per month compared with placebo, as well as the significant reductions in the mean monthly attack rate for secondary endpoints compared to placebo. The most important safety concern associated with lanadelumab is hypersensitivity. The proposed labeling includes a warning and precaution that hypersensitivity reactions have been observed.

It is expected that lanadelumab will be prescribed by allergists and clinical immunologists who have experience treating patients with HAE.

Based on the observed benefit of lanadelumab, the serious nature of the disease, and a risk profile that will not require any risk mitigation beyond labeling, DRISK is not recommending a REMS for the management of the risks of lanadelumab therapy.

9 Conclusion & Recommendations

Based on the available information a REMS is not necessary to ensure the benefits of lanadelumab outweigh the risks.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

- ¹ Cicardi M, Zuraw B. Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis. In:UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham, MA 2018.
- ² Cicardi M, Zuraw B. Hereditary angioedema: Pathogenesis and diagnosis. In:UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham, MA 2018.
- ³ Cicardi M, Zuraw B. Hereditary angioedema: General care and long-term prophylaxis. In:UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham, MA 2018.
- ⁴ Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. *Ann Allergy Asthma Immunol* 2015; 114:281-288.
- ⁵ Dyax Corp. Summary of Clinical Efficacy, BLA 761090, December 26, 2017.
- ⁶ Draft NDA/BLA Multi-disciplinary Review and Evaluation, BLA 761090, August 11, 2018.
- ⁷ Dyax Corp. Summary of Clinical Safety, BLA 761090, December 26, 2017.
- ⁸ Dyax Corp. 120-Day Safety Update, BLA 761090, April 24, 2018.

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