CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	217202
PDUFA Goal Date	May 31, 2023
OSE TTT #	2022-2278
Reviewer Name	Brian Caruth, Pharm.D., BCPS
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Review Completion Date	May 30, 2023
Subject	Evaluation of Need for a REMS
Established Name	Landiolol
Name of Applicant	AOP Orphan Pharmaceuticals GmbH (Agios)
Therapeutic Class	Beta adrenergic blocker
Formulation(s)	Lyophilized powder for injection
Dosing Regimen	Initiate at 9.3 mcg per kg per minute and increase by 9.3 mcg per kg per minute every 10 minutes to a maximum of 37.3 mcg per kg per minute according to the heart rate and cardiovascular status of the patient; up to 24 hours. Dose reduction is necessary for patients with impaired cardiac function.

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) landiolol is necessary to ensure the benefits outweigh its risks. AOP Orphan Pharmaceuticals GmbH submitted a New Drug Application (NDA) 217202 for landiolol with the proposed indication for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. Landiolol is associated with an increased risk for hypotension. The Applicant did not submit a proposed REMS or risk management plan with this application.

The recommended regulatory action at this time per the interdisciplinary review team is a complete response. This recommendation is due to manufacturing deficiencies at the drug product site.

Based on the available data, DRM and the Division of Cardiology and Nephrology (DCN) agree that there are no safety issues that require a REMS. If new safety information becomes available DRM should be consulted, to reassess the need for a REMS.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) landiolol is necessary to ensure the benefits outweigh its risks. AOP Orphan Pharmaceuticals GmbH submitted a New Drug Application (NDA) 217202 for landiolol with the proposed indication for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Landiolol, a new molecular entity[a], is a beta adrenergic blocker proposed for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. A beta adrenergic blocker antagonizes the effects of sympathetic neurotransmitters by competing for $beta_1$ and $beta_2$ receptor binding sites. $Beta_1$-selective adrenergic blockers primarily block receptors located in cardiac tissue. Some beta adrenergic blockers demonstrate intrinsic sympathomimetic activity (ISA) providing low-grade beta stimulation at rest but acting as typical beta adrenergic blockers when sympathetic activity is high. Landiolol is a $beta_1$-selective adrenergic blocker that exhibits no intrinsic sympathomimetic activity.

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

Landiolol is proposed to be available as 280 mg of lyophilized powder in a single dose vial to be reconstituted with 50 mL of 0.9% sodium chloride or 5% dextrose for intravenous administration. The recommended starting dose for patients with normal cardiac function is 9.3 mcg per kg per minute. Dose escalation of 9.3 mcg per kg per minute every 10 minutes to a maximum of 37.3 mcg per kg per minute according to the heart rate and cardiovascular status of the patient may be continued up to 24 hours. Dose reduction is necessary for patients with impaired cardiac function. Table 1 lists the recommended dose adjustments for landiolol therapy. Duration of treatment with landiolol is expected to be short-term (less than 24 hours) and likely administered in a monitored inpatient setting.[b] Landiolol is currently approved in Japan (2002) and Europe (2016).

Table 1: Dose Titration for Landiolol

Cardiac Function	Landiolol Dose Titration		
	Initiate	Titrate	Maximum Dose
Normal	9.3 mcg/kg/min	9.3 mcg/kg/min every 10 minutes	37.3 mcg/kg/min
Impaired	(b) (4) mcg/kg/min	(b) (4) mcg/kg/min every 15 minutes	(b) (4) mcg/kg/min

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 217202 relevant to this review:

- 05/30/2022: NDA 217202 received for landiolol
- 11/17/2022: Mid-Cycle meeting held via teleconference and FDA informed the Applicant that no safety issues that may require a REMS for landiolol have been identified
- 03/14/2023: Late-Cycle meeting held via teleconference and FDA informed the Applicant that no safety issues that may require a REMS for landiolol have been identified

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Tachyarrhythmias are abnormal heart rhythms with a ventricular rate of 100 or more beats per minute (BPM). Supraventricular tachyarrhythmia (SVT), hypertension and tachycardia in the perioperative setting, and acute ischemic heart disease are generally agreed to require rapid attention and treatment. Prolonged tachyarrhythmia or hypertension can result in significant morbidity, such as cerebrovascular events, myocardial infarction, and other end-organ damage.[1,c] Intraoperative tachyarrhythmias and bradyarrhythmias are common; nearly 11% of patients experience abnormal heart rate (HR) or rhythm during general anesthesia.

The epidemiology of SVT, including its frequency, patterns, causes, and effects, is imprecisely defined because of incomplete data and failure to discriminate among atrial fibrillation (AF), atrial flutter (AFL), and other supraventricular arrhythmias. The best available evidence indicates that the prevalence of SVT in the general population is 2.29 per 1000 persons.[2]

[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.*

3.2 Description of Current Treatment Options

Nonpharmacologic interventions for the acute management of SVT may include direct-current cardioversion, vagal maneuvers, or carotid sinus massage. Current FDA-approved treatment options for SVT include beta adrenergic blockers (selective and non-selective), non-dihydropyridine calcium channel blockers, and adenosine. Off-label treatment options recommended in treatment guidelines include metoprolol and amiodarone (Table 2). The risk of hypotension is included in the labeling for beta adrenergic blockers, non-dihydropyridine calcium channel blockers, and amiodarone. Labeling also includes recommendations for monitoring and dose adjustments if hypotension occurs. The risk of hypotension is not listed for adenosine as the bolus dose usually has no systemic hemodynamic effects. While various treatment options for the acute management of SVT are available, longer acting agents may present as a difficult clinical problem in the perioperative management of hypertension and tachycardia[3] and a lack of rapid acting pharmacologic therapies represent an unmet medical need.

Table 2: Pharmacologic Treatment of Intraoperative Arrhythmias[4]

Therapeutic Class	Medication	Recommended Dose (Intravenous)
Beta Adrenergic Blocker	Metoprolol	1 to 5 mg bolus over two minutes; may repeat two times
	Esmolol	1 mg/kg bolus, followed by 150 mcg/kg per minute infusion
Calcium Channel Blocker	Verapamil	0.07 to 0.15 mg/kg (usually 5 to 10 mg/dose [maximum 10 mg]) bolus over two minutes; may repeat once every 15 to 30 minutes if necessary. If no response, start 0.005 mg/kg/min infusion.
	Diltiazem	0.25 mg/kg bolus over two minutes; start 5 to 15 mg/hour infusion
Antiarrhythmic Agent	Adenosine	6 mg rapid bolus; if not effective within one to two minutes, give 12 mg; if not effective within 1 to 2 minutes, may repeat 12 mg
	Amiodarone	150 mg bolus over 10 minutes, then start infusion at 1 mg/min for six hours, followed by 0.5 mg/min for 18 hours

4 Benefit Assessment

The efficacy of landiolol for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter relies on six randomized placebo-controlled studies and two randomized active-controlled studies with diltiazem and digoxin exclusively from the published literature. The eight studies represented clinical data without individual patient-level data, from multiple sites in China and Japan. The subject population in the eight studies were similar to the target patient population who might receive landiolol treatment in the US. The Applicant did not conduct a relative bioavailability study comparing the proposed landiolol formulation for this application with the landiolol formulations in the eight studies evaluated for effectiveness, however significant differences between the proposed and studied formulations are not expected. Table 3 summarizes the eight clinical studies from the published literature.

Table 3: Summary of Studies Contributing to the Efficacy Data of Landiolol

Author (Year)	Duration and Dose Evaluated	Subjects	Primary Endpoint
Randomized Placebo-Controlled Studies			
Kato (1997)	250 mcg/kg bolus then 80 mcg/kg/min for 10 minutes	108	decrease in HR at 11 minutes
Yoshiya (1997)	125 mcg/kg bolus then 40 mcg/kg/min for 10 minutes	284	decrease in HR at 5 minutes
Yoshiya (2002)	125 mcg/kg bolus then 40 mcg/kg/min for 10 minutes	58	decrease in HR at 11 minutes
Tanaka (2008)	30 – 125 mcg/kg bolus then 10 – 40 mcg/kg/min for 10 minutes	12	decrease in HR ≥ 20% and HR < 100 BPM at 11 or 22 minutes
Taenaka/Kikawa (2013)	30 – 125 mcg/kg bolus then 10 – 40 mcg/kg/min for 10 minutes	165	decrease in HR ≥ 20% and HR < 100 BMP at 11 or 22 minutes
Xiao (2014)	125 mcg/kg bolus then 40 mcg/kg/min for 10 minutes	240	Subjects who received esmolol when decrease in HR ≤ 10% at 5 minutes
Randomized Active-Controlled Studies			
Sakamoto (2012)	0.5 – 40 mcg/kg/min for 24 hours; diltiazem 0.25 mg/kg bolus then 3 – 15 mg/hour	71	Conversion to sinus rhythm at 8 hours
Nagai (2013)	1 – 40 mcg/kg/min for 2 – 48 hours; digoxin 0.25 mg bolus	214	decrease in HR ≥ 20% and HR < 110 BPM at 2 hours

During a Type B Pre-NDA Meeting on January 25, 2022, the Division and the Applicant agreed upon a post-hoc primary effectiveness endpoint for landiolol therapy to facilitate comparison of treatment effectiveness across the published studies in patients with SVT. The endpoint was the responder analysis composite of a decrease in HR ≥ 20%, or achievement of HR ≤ 100 BPM, or terminated paroxysm of SVT. Despite different primary outcomes in the eight studies, all studies evaluated the effect of landiolol on HR in the short-term setting.

The clinical reviewer concluded that the totality of effectiveness data from the eight studies supported the benefit of landiolol. This determination relied on the statistically and clinically significant greater proportion of subjects with SVT and tachycardia treated with landiolol that had a decreased HR compared to placebo. Furthermore, the treatment effects were generally large and efficacy assessment did not rely on complicated statistical methodologies or formal meta-analysis.

5 Risk Assessment & Safe-Use Conditions

The primary safety review of landiolol relies on the adverse event data in the published literature from eight clinical studies. Despite the lack of individual patient-level safety data, the safety database represents 568 landiolol-exposed subjects. Adequacy of the safety database is also supported by the lack of additional unexpected adverse events in the postmarketing surveillance data from the past five and a half years representing exposure in an estimated (b) (4) subjects.

Adverse event rates were evaluated from the randomized, placebo-controlled studies rather than the overall safety database because the patient population likely to receive landiolol in clinical practice was considered more representative of this subgroup. The most common adverse event in the randomized, placebo-controlled studies was hypotension (9.9% [44/445]) compared to placebo (1.3% [5/395]). The

rates of bradycardia, cardiogenic shock, heart failure, and bronchospasm were low and did not suggest an additional substantial effect from landiolol.

One death occurred in a subject that received landiolol and one death occurred in a subject that received digoxin. The death in the landiolol group was due to an exacerbation of heart failure. The subject died 31 hours after completing landiolol therapy. The death in the digoxin group was due to sinus arrest. The clinical reviewer assessed the overall risk of landiolol associated mortality to be low and focused on hypotension, the most common and serious adverse event associated with landiolol therapy.

5.1 HYPOTENSION

Hypotension is consistent with the mechanism of action of landiolol and known to be associated with other beta adrenergic blockers.[d] Data from the safety database demonstrated a temporal change in blood pressure (BP) that was consistent with the known pharmacokinetics of landiolol, with onset within five minutes of initiation of landiolol administration and resolution of BP effects within 30 minutes after landiolol discontinuation in the majority of patients. The risk of hypotension varied by the clinical trial population, but no specific predictors of increased risk of hypotension were identified. In the randomized, placebo-controlled studies, the absolute risk difference for hypotension between landiolol and placebo was 8.6% and a relative risk of 7.6 was observed with landiolol treatment.

The clinical review team agreed with the Applicant's proposal to address the risk of hypotension in the Warnings and Precautions and Adverse Reactions sections of the label. Labeling also includes recommendations for monitoring blood pressure and dose adjustments if hypotension occurs.

The clinical reviewer concluded the safety profile of landiolol is favorable for the short-term reduction of ventricular rate in patients with SVT including AF and AFL and the overall benefit-risk profile appears acceptable.

6 Expected Postmarket Use

Landiolol is likely to be prescribed for short-term use (less than 24 hours) in a monitored inpatient setting by anesthesiologists and cardiologists familiar with supraventricular tachycardia therapy. Prescribers are expected to closely monitor and frequently reassess patients for signs and symptoms of hypotension and optimize therapy accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for landiolol beyond routine pharmacovigilance and labeling.

[d] 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 landiolol citing the efficacy and safety data in the published literature from eight clinical studies, short-term use in a specific patient population, and an adequately favorable benefit-risk profile.

Tachyarrhythmias are abnormal heart rhythms with a ventricular rate of 100 or more BPM. SVT, hypertension and tachycardia in the perioperative setting, and acute ischemic heart disease are generally agreed to require rapid attention and treatment. Prolonged tachyarrhythmia or hypertension can result in significant morbidity, such as cerebrovascular events, myocardial infarction, and other end-organ damage.

The efficacy of landiolol for the short-term reduction of ventricular rate in patients with SVT including AF and AFL relied on eight clinical studies from the published literature. All studies evaluated the effect of landiolol on HR in the short-term setting. A statistically and clinically significant greater proportion of subjects with SVT and tachycardia treated with landiolol had a decreased HR compared to placebo. The treatment effects were generally large and efficacy assessment did not rely on complicated statistical methodologies or formal meta-analysis.

The serious risk associated with landiolol is an increased risk for hypotension. In general, healthcare providers who treat patients with SVT should be familiar with monitoring and treating the risk of hypotension. The duration of treatment for patients receiving landiolol is expected to be short-term (less than 24 hours) and likely administered in a monitored inpatient setting. Information regarding these risks and appropriate monitoring will be included in the Warnings and Precautions and Adverse Reactions sections in labeling. The clinical review team also stated that the safety data do not indicate need for a specific REMS to mitigate the risks for landiolol and that overall, it has a favorable safety profile. Therefore, this reviewer is not recommending a REMS for the management of the risks of landiolol therapy.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of landiolol outweigh the risk for hypotension. Information about this risk will be communicated in labeling using the Warnings and Precautions and Adverse Reactions sections. In general, we expect healthcare providers who treat patients with SVT are familiar with monitoring and treating the risk of hypotension.

However, the recommended regulatory action at this time per the interdisciplinary review team is a complete response. This recommendation is due to manufacturing deficiencies at the drug product site.

Based on the available data, there were no unique safety issues that require a REMS for landiolol as compared with the risks associated with other beta adrenergic blocker therapies. If new safety information becomes available, please consult DRM and we can re-evaluate the need for a REMS.

10 Appendices

10.1 References

[1] Garnock-Jones KP. Esmolol: a review of its use in the short-term treatment of tachyarrhythmias and the short-term control of tachycardia and hypertension. Drugs. 2012;72(1):109-132.

[2] Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016;133(14):e506-e574.

[3] Reves JG, Flezzani P. Perioperative use of esmolol. American Journal of Cardiology. 1985;56(11):57F-62F.

[4] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130:e199.

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