CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Executive Summary

Date	15 November, 2024
From	Theodore Carver, Ph.D.
Through	Hylton Joffe, MD, MMSc
Priority or Standard	Standard
NDA/BLA # and Supplement#	217202
Applicant	AOP Orphan Pharmaceuticals GmbH
Date of Submission	29 May 2024
PDUFA Goal Date	29 November, 2024
Proprietary Name	RAPIBLYK
Established or Proper Name	Landiolol
Dosage Form(s)	Intravenous Infusion
Applicant Proposed Indication(s)/Population(s)	Short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter
Applicant Proposed Dosing Regimen(s)	1. For patients with normal cardiac function, titrate using ventricular rate at 10-minute intervals: start at 10 mcg/kg/min; adjust dose as needed up to 40 mcg/kg/min in 10 mcg/kg/min increments to achieve desired reduction of ventricular rate. 2. For patients with impaired cardiac function titrate using ventricular rate at 15-minute intervals: Start at 1 mcg/kg/min, adjust dose as needed up to (b) (4) mcg/kg/min in 1 mcg/kg/min increments to achieve desired reduction of ventricular rate.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Recommended Dosing Regimen(s)	Same as Applicant's proposed dosing regimen: 1. <u>Patients with normal left ventricular myocardial contractile function</u>: starting dose of 10 mcg/kg/min for 10 min, followed by titration by 10 mcg/kg/min every 10 minutes to a maximum dose of 40 mcg/kg/min; and 2. <u>Patients with reduced left ventricular myocardial contractile function</u>: starting dose of 1 mcg/kg/min for 15 min, followed by titration by 1 mcg/kg/min every 15 minutes to a maximum dose of (b) (4) mcg/kg/min.

CDER Cross Discipline Team Leader Review
Theodore Carver, Ph.D.
NDA 217202- Landiolol Hydrochloride

This secondary review is based on the following reviews as well as consults and meeting minutes:

Materials Reviewed		
Reviews		
#	**Discipline (Date)**	**Reviewers**
1	Clinical Pharmacology (9/20/2024)	Li Wang, PhD; Doanh C. Tran
2	Pharmacology / Toxicology Review (10/14/2024), Division of Pharmacology/Toxicology Office of Cardiology, Hematology, Endocrinology, & Nephrology	Paul Grimm, Ph.D.; David Carlson, PhD
4	Integrated Quality Review (10/11/2024), Office of Pharmaceutical Quality	Dan Berger, PhD; Ted Carver, Ph.D. (Drug Product and Labeling) Allison Aldridge, PhD; Rose Xu, Ph.D. (Manufacturing) Ted Carver, PhD (Application Technical Lead)
5	Labeling Reviews (10/30/2024, 11/8/2024, and 11/14/2024), Division of Medication Error Prevention and Analysis 2 (DMEPA 2)	Christina Topper PharmD and Nicole Iverson, PharmD, BCPS
6	Proprietary Name Review (8/27/2024), Division of Medication Error Prevention and Analysis 2 (DMEPA 2)	Jody Kundreskas, PharmD., Nicole Iverson, PharmD, BCPS and Hina Mehta, PharmD
7	Labeling Review (11/14/2024), Office of Prescription Drug Promotion (OPDP)	Meena Savani and Sapna Shah

Conclusions on the Benefit-Risk Assessment

This is the second review cycle for landiolol. The application received a Complete Response letter on the first review cycle due to CMC deficiencies. For this NDA 217202 resubmission, reference is made to the CDTL review previously authored by Dr. Fred Senatore (CDTL review in DARRTS, dated May 31, 2023) and the benefit-risk conclusions in that review. There were no changes in the NDA that would affect the assessment of benefit and risk from the clinical perspective other than the resolution of the CMC deficiencies as outlined below. In addition, reference is made to the Benefit-Risk Framework (BRF) previously authored by Mitchell Psotka, MD, PhD., in the clinical review (DARRTS, dated May 21, 2023), which serves as the BRF for this application.

The Applicant provided literature-based evidence from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials to support the NDA. As the data from 1 of the active-

controlled (i.e., diltiazem) clinical trials were considered uninterpretable (Sakamoto, 2012), it was excluded as evidence to support the proposed indication. The remaining data showed that landiolol hydrochloride was effective in the short-term reduction of heart rate (HR) when treating patients with supraventricular tachycardia (SVT), including atrial fibrillation (AF) and atrial flutter (AFL). Effectiveness in reducing HR with these conditions was also observed in patients with concomitant heart failure (HF).

Since the CMC deficiencies identified in the previous review cycle have been resolved by the Applicant, the overall recommendation is approval of landiolol hydrochloride for the proposed indication. The manufacturing facilities remain adequate to support approval.

Background

Landiolol is an ultra-short-acting β1-selective blocking agent. It is rapidly hydrolyzed to an inactive form by both carboxylesterase in the liver and pseudocholinesterase in the plasma, resulting in an elimination half-life of about 4 minutes. The selectivity for the β-1-receptor is 255 times that for the β-2-receptor. Landiolol inhibits the positive chronotropic effects of the catecholamines epinephrine and norepinephrine on the heart, where β-1-receptors are predominantly located. Landiolol, as with other beta-blockers, is thought to reduce sympathetic drive, resulting in reduction of HR, a decrease in spontaneous firing of ectopic pacemakers, slowing of conduction, and an increase in the refractory period of the AV node.

Landiolol hydrochloride was approved in Europe (as Rapibloc) and Japan (as Onoact), at intravenous doses ranging from 1 and 40 mcg/kg/min, to reduce ventricular rate in patients with SVT, including AF and AFL. Landiolol has not been approved in the USA and is therefore considered a new molecular entity.

This 505(b)(2) application relies on published literature to establish effectiveness and safety and for certain nonclinical pharmacology/toxicology studies. The Applicant did not have access to patient-level data.

Discipline Reviews

Clinical Pharmacology

The clinical pharmacology team previously recommended approval of this NDA with a post marketing requirement (PMR) to evaluate the potential of landiolol and its M1 metabolite to inhibit drug transporters including P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, OAT1, and OAT3, and the Applicant previously agreed to this PMR. For this NDA resubmission, the clinical pharmacology team (b) (4) for the assessment of the inhibitory effect of landiolol and its metabolite M1 on these drug transporters. The proposed (b) (4) appears acceptable, and approval of NDA 217202 is recommended from the clinical pharmacology perspective.

Clinical Review

The clinical review was previously conducted by Mitchell Psotka, MD, PhD, and there have been no changes in the supporting information; therefore, the clinical team continues to recommend approval of NDA 217202.

CMC Review

The CMC review of the NDA resubmission was focused on information provided to resolve the drug product and manufacturing deficiencies identified in the previous Complete Response letter. This review was performed by Dan Berger, PhD (drug product and labeling) and Allison Aldridge, PhD (manufacturing). The reviews for all other disciplines remain adequate; for more information, see the Integrated Quality Assessment dated May 30th, 2023.

With respect to the drug product review, (b) (4) was identified as an impurity (b) (4), and the maximum daily exposure to this impurity based on test data submitted in the original NDA exceeded the FDA-recommended acceptable daily intake limit ((b) (4) ng/day) recommended by the nonclinical review team in consultation with the computational toxicology consultation service (CTCS) during the review of the original NDA. After the complete response was issued for NDA 217202, the AI limit for (b) (4) was re-evaluated based on a (b) (4) as described in the updated FDA Guidance for Industry (b) (4) The revised AI limit was determined by CTCS to be (b) (4) ng/day. Based upon an agreed upon higher AI limit of (b) (4) ng/day in discussions between the Agency and the Applicant (see also minutes from Type A meeting held on October 27, 2023), the Applicant's proposed acceptance criterion of (b) (4) ppb was determined to be acceptable in the CMC review of the resubmitted NDA. Additional stability data in the NDA resubmission confirmed that the proposed shelf-life of 24 months at 25°C is acceptable, including the levels of (b) (4) through the shelf life.

A second deficiency in the drug product review of the original NDA was inadequate acceptance criteria for the (b) (4) test in the drug product lot release specification. The Applicant proposed revised acceptance criteria for the (b) (4) tests, and the drug product review determined the final specification to be acceptable to ensure product quality.

With respect to the manufacturing review, the review of the original NDA identified outstanding deficiencies in the manufacturing process, including (b) (4) and limits, in-process controls, and (b) (4) limits. The manufacturing review of the NDA resubmission determined that all manufacturing deficiencies have been adequately addressed.

Therefore, approval of NDA 217202 is recommended from the overall quality/CMC perspective.

Pharmacology/Toxicology

The pharmacology/toxicology review of the NDA resubmission was performed by Paul Grimm, Ph.D. The previous review of the original NDA concluded that the nonclinical data submitted by

the Applicant along with the publicly available literature supported the safety of the proposed clinical dosing regimen for the landiolol 300 mg injection formulation. Therefore, the only outstanding review issue was the limit for the (b) (4) impurity in the drug product. As indicated in the summary of the CMC review, the pharmacology/toxicology review team agreed upon a revised acceptable daily intake limit of (b) (4) ng/day for this impurity, and based on this limit, the proposed acceptable criteria and observed impurity levels are acceptable for the drug product. Therefore, approval of NDA 217202 is recommended from the pharmacology/toxicology perspective.

Labeling and Proprietary Name Review

The review of the labeling performed by the Division of Medication Error Prevention and Analysis and the Office of Prescription Drug Promotion concluded that the labeling is acceptable with revisions, and final communications regarding proposed revisions to the labeling from all disciplines are ongoing at the time of this review.

The Applicant submitted a new proposed proprietary name, Rapiblyk, for review on May 29, 2024. This proposed proprietary name was reviewed from a safety and misbranding perspective by Jody Kundreskas, PharmD and Nicole Iverson, PharmD. and was determined to be acceptable. The EU trade name is RAPIBLOC®.

Postmarketing Requirements and Pediatric Study Plan

As indicated in the review of the original NDA, the division agreed with the Applicant's Initial Pediatric Study Plan (IPSP). The preliminary postmarketing requirements (PMRs) that were communicated to the Applicant are as follows (November 6, 2024):

1. Conduct an in vitro assessment to evaluate the potential of landiolol and its M1 metabolite to inhibit drug transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 2, multidrug and toxin extrusion (MATE) proteins (MATE1, MATE2-K), organic anion transporter (OAT) 1, and OAT3. Additional in vivo studies may be needed depending on the results of the in vitro assessment.

2. The "Multicenter, open-label study to investigate the effectiveness and safety of AOP Landiolol in controlling supraventricular tachycardia in pediatric patients" (LANDI-PED) referenced in the agreed iPSP is complete (b) (4) . Submission of the final CSR and any proposed label changes are requested by December 31, 2024.

Recommended Regulatory Action

NDA 217202 for Rapiblyk (landiolol) for injection is recommended for approval by all review disciplines because there are no outstanding deficiencies. The clinical team also concludes that the benefits outweigh the risks. I agree with this assessment and recommend approval of this NDA.

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APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THEODORE E CARVER
11/20/2024 05:35:39 PM

HYLTON V JOFFE
11/22/2024 10:55:29 AM
I concur with approval. This memorandum serves as the decisional memorandum on the application.

Cross-Discipline Team Leader Executive Summary

Date	01 MAY 2023
From	Fred Senatore MD, PhD, FACC
Priority or Standard	Standard
NDA/BLA # and Supplement#	217202
Applicant	AOP Orphan Pharmaceuticals GmbH
Date of Submission	31 MAY 2022
PDUFA Goal Date	31 MAY 2023
Proprietary Name	----not determined----
Established or Proper Name	Landiolol hydrochloride
Dosage Form(s)	Intravenous Infusion
Applicant Proposed Indication(s)/Population(s)	Short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter
Applicant Proposed Dosing Regimen(s)	1. For patients with normal cardiac function, titrate using ventricular rate at 10-minute intervals: start at 10 mcg/kg/min; adjust dose as needed up to 40 mcg/kg/min in 10 mcg/kg/min increments to achieve desired reduction of ventricular rate. 2. For patients with impaired cardiac function titrate using ventricular rate at 15-minute intervals: Start at 1 mcg/kg/min, adjust dose as needed up to (b) (4) mcg/kg/min in 1 mcg/kg/min increments to achieve desired reduction of ventricular rate.
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Recommended Dosing Regimen(s)	Same as Applicant's proposed dosing regimen: 1. Patients with normal left ventricular myocardial contractile function: starting dose of 10 mcg/kg/min for 10 min, followed by titration by 10 mcg/kg/min every 10 minutes to a maximum dose of 40 mcg/kg/min; and 2. Patients with reduced left ventricular myocardial contractile function: starting dose of 1 mcg/kg/min for 15 min, followed by titration by 1 mcg/kg/min every 15 minutes to a maximum dose of (b) (4) mcg/kg/min.

CDER Cross Discipline Team Leader Review
Fred Senatore MD, PhD, FACC
NDA 217202- Landiolol Hydrochloride
This secondary review is based on the following reviews as well as consults and meeting minutes:

Materials Reviewed		
Reviews		
#	Discipline (Date)	Reviewers
1	Clinical Pharmacology	Li Wang, PhD; Snehal Samant, PhD
2	Pharmacology / Toxicology	Feleke Eshete, PhD; David Carlson, PhD
3	Clinical	Mitchell Psotka, MD, PhD
4	CMC	Daniel Jansen, PhD (Drug Substance) Dan Berger, PhD (Drug Product and Labeling) Allison Aldridge, PhD (Manufacturing) Joan Zhao, PhD (Biopharmaceutics) Ted Carver, PhD (supervisor)

Conclusions on the Benefit-Risk Assessment

Reference is made to the Benefit-Risk Framework (BRF) authored by Mitchell Psotka, MD, PhD., in the clinical review, which serves as the BRF for this application. The Applicant provided literature-based evidence from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials to support the NDA. As the data from 1 of the active-controlled (i.e., diltiazem) clinical trials were considered uninterpretable (Sakamoto, 2012), it was excluded as evidence to support the proposed indication. The remaining data showed that landiolol hydrochloride was effective in the short-term reduction of heart rate (HR) when treating patients with supraventricular tachycardia (SVT), including atrial fibrillation (AF) and atrial flutter (AFL). Effectiveness in reducing HR with these conditions was also observed in patients with concomitant heart failure (HF).

The clinical benefit in reducing HR is manifest in how a patient feels (i.e., reduction in palpation, and/or shortness of breath). In the setting of coronary artery disease, which is very likely in patients presenting with SVT, AF, AFL, and HF, beta-blockade mediated reduction in HR has a cardioprotective benefit, although this NDA did not evaluate these clinical benefits.

The submitted publications showed reversible hypotension as the only safety signal. There were 2 cases of bradycardia in the landiolol arms (0.2%, n=2/962) and 1 case of bradycardia in the placebo arms (0.2%, n=1/799) of the combined placebo-controlled trials (not sufficient to classify this as a safety signal). No other known beta-1-blocker risks (e.g., fatigue, nausea, dizziness, constipation) were reported in the submitted literature.

The literature-based clinical evidence of effectiveness was substantial and outweighs the risks, warranting a clinical recommendation to approve landiolol for the Applicant's proposed indication: short-term reduction of ventricular rate in patients with SVT including AF and AFL.

However, approval is not possible at this time because CMC issues led to that discipline's recommendation for a Complete Response (CR). The key issue was an unacceptable level of (b) (4), a carcinogenic substance. Another issue was the Applicant's proposal to (b) (4) to facilitate meeting the requirements of the (b) (4) specification. The Complete Response letter will include requirements involving product quality and manufacturing needed to reconcile the CMC deficiencies and thus facilitate ultimate approval of landiolol hydrochloride for the proposed indication. Recent inspection of the manufacturing facility was assessed as adequate.

Product Introduction

Landiolol is an ultra-short-acting β1-selective blocking agent. It is rapidly hydrolyzed to an inactive form by both carboxylesterase in the liver and pseudocholinesterase in the plasma, resulting in an elimination half-life of about 4 minutes. The selectivity for the β-1-receptor is 255 times that for the β-2-receptor. Landiolol inhibits the positive chronotropic effects of the catecholamines adrenaline and noradrenaline on the heart, where β-1-receptors are predominantly located. Landiolol, as with other beta-blockers, is thought to reduce sympathetic

drive, resulting in reduction of HR, a decrease in spontaneous firing of ectopic pacemakers, slowing of conduction, and an increase in the refractory period of the AV node.

Landiolol hydrochloride was approved in Europe (as Rapibloc) and Japan (as Onoact), at intravenous doses ranging from 1 and 40 mcg/kg/min, to reduce ventricular rate in patients with SVT, including AF and AFL. Landiolol has not been approved in the USA and is therefore considered a new molecular entity.

This 505(b)(2) application relies on published literature to establish effectiveness and safety and for certain nonclinical pharmacology/toxicology studies. The Applicant did not have access to patient-level data.

The Applicant proposes two dosing schemes based on the clinical context of the patient with SVT to be treated:

1. Patients with normal left ventricular myocardial contractile function: starting dose of 10 mcg/kg/min for 10 min, followed by titration by 10 mcg/kg/min every 10 minutes to a maximum dose of 40 mcg/kg/min; and
2. Patients with reduced left ventricular myocardial contractile function: starting dose of 1 mcg/kg/min for 15 min, followed by titration by 1 mcg/kg/min every 15 minutes to a maximum dose of (b) (4) mcg/kg/min.

This regimen is acceptable, as explained below. The submitted data support infusion for up to 24 hours.

Discipline Reviews

Clinical Pharmacology

The clinical pharmacology review authored by Li Wang, PhD, and Snehal Samant, PhD, reported the Applicant has conducted four clinical PK/PD studies (three in healthy subjects and one in patients), and three in vitro studies. The clinical pharmacology review also referenced the same 8 eight publications referenced in the clinical review.

Several observations from the clinical pharmacology review were noted:

- The Applicant did not conduct a relative bioavailability study comparing Onoact® 50 mg and Landiolol HCl 300 mg formulations. Given the high-water solubility of landiolol, relatively simple formulations, similar excipients and active to inactive ingredient ratio, significant differences in the bioavailability are not expected for the parenteral solution intended solely for administration by intravenous injection.
- The effect of renal impairment on the PK of landiolol has not been tested. However, adjustment of the dose of landiolol in patients with renal impairment is not warranted as landiolol is used for single iv infusion up to 24 hours and renal excretion is not the major elimination pathway for landiolol (<10%).
- The Applicant referenced a scientific publication by Takahata et al. (2005) to provide information on the effect of hepatic impairment on the PK of landiolol. Because most of

the subjects with hepatic impairment (5 out of 6) in the study had Child-Pugh Class A, the effect of moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) on the PK of landiolol is not clear. A clinical study has not been conducted to date to characterize this effect. As landiolol is proposed to be used as single dose in patients with an urgent clinical situation and the terminal half-life is very short, no PMR is required.

- The Applicant did not investigate the inhibitory effect of landiolol and its metabolite M1 on the activity of multiple drug transporters such as P-glycoprotein, breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OAT1, OAT 3, OATP1B1, OATP1B3), organic cation transporter (OCT2), multidrug and toxin extrusion proteins 1 and 2-k (MATE1, MATE2-K), OAT1, and OAT3. A PMR was recommended to the Applicant to conduct an in vitro assessment to evaluate the potential of landiolol and the M1 metabolite to inhibit these transporters and aid in determining the need for any in-vivo drug-drug interaction study. The Applicant has agreed to the PMR.

The clinical pharmacology review team recommended approval of the NDA. Labeling recommendations included:

- (b) (4)
- Section 12.2 Pharmacodynamic: Revising the content (b) (4). When revising this section, the Applicant should reference the requirements found in the FDA Guidance on Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format.

Pharmacology/Toxicology

The pharmacology/toxicology review was authored by Feleke Eshete, PhD (supervisor/team leader David Carlson, PhD). A maximum clinical dose of landiolol 40 µg/kg/min, equivalent to 57.6 mg/kg/day, is proposed for marketing. The nonclinical pharmacology/toxicology safety evaluation included a rat single dose study of 24 hours of continuous intravenous infusion of doses of 250, 500, & 1,000 mg/kg, and a 4-week dog study of 24 hours-a-day of continuous infusion at 0.04 mg/kg/min (58 mg/day), 0.2 mg/kg/min (288 mg/day), and 1 mg/kg/min (1,440 mg/day). The animal exposures at the NOAEL doses were compared with the exposure in patients with tachycardic AF or AFL [protocol# LDLL600.201] who received the recommended clinical dosing regimen. There was a 2-fold safety margin with the maximum recommended clinical dose compared to the tolerated infusion in rats, and a very high safety margin (136-fold) relative to the NOAEL exposure in the 4-week, 24-hr-a-day infusion study in dogs that simulated prolonged exposure to the proposed dosing regimen.

The pharmacology/toxicology reviewers concluded the nonclinical data submitted by the Applicant along with the publicly available literature supported the safety of the proposed

clinical dosing regimen for the landiolol 300 mg injection formulation and recommend approval from a nonclinical perspective once the (b) (4) impurity is controlled at an acceptable level.

Clinical Review

The clinical review, written by Mitchell Psotka, MD, PhD, reported that the Applicant relied on 8 publications, without patient-level data. Six publications described randomized placebo-controlled trials and 2 publications described randomized active-controlled trials with diltiazem and digoxin, respectively. As the data from 1 of the active-controlled (i.e., diltiazem) clinical trials were considered uninterpretable (Sakamoto, 2012), it was excluded as evidence to support the proposed indication.

The proposed indication (i.e., control of HR in the setting of SVT including AF and AFL) is consistent with a key clinical practice paradigm of controlling the ventricular response to supraventricular tachyarrhythmias. In patients with underlying coronary artery disease, which is common in patients with SVT, this approach of heart rate control can reduce the risk of cardiac ischemia by lowering cardiac workload. The effect of HR reduction on clinical outcomes, including among those without underlying coronary artery disease, has never been tested because of widespread clinical practice that accepts that rapid ventricular response will be detrimental if left untreated.

There was inconsistency amongst the published papers that served as the basis of the landiolol NDA with respect to the intention-to-treat populations, posology, duration of treatment, primary efficacy endpoints, and how safety data were collected. Given the heterogeneity of the publications supporting this NDA, the Applicant proposed a post-hoc primary efficacy endpoint of a ≥20% reduction from baseline in HR for patients with SVT, a decrease in HR to <100 bpm, or conversion to sinus rhythm. This was precisely the treatment effect for which esmolol was approved in 1986 following a Cardiovascular and Renal Drugs Advisory Committee (AC) meeting on September 29, 1986. It was believed by the AC that this treatment effect in the in-patient setting was a clinically meaningful surrogate, as discussed in Section 5.2 Review Strategy of Dr. Psotka's clinical review. Despite the disparate primary endpoints utilized in each of the randomized controlled trials submitted to support the NDA, each trial included as a primary or secondary endpoint the effect of landiolol on HR in the short-term setting thus facilitating an integrated review of the trial HR data. However, each trial was judged on its own merit regarding their respective primary efficacy endpoints. Of note, there is a consistent finding of effectiveness of landiolol across 7 randomized, controlled clinical trials, which mitigates concerns for type 1 error that can arise with post-hoc efficacy endpoints. In addition, there is well-known mechanistic, efficacy and safety data with the class of beta-blockers, which have been marketed for decades. While these other data are not critical for concluding that there is safety and substantial evidence of effectiveness for landiolol, they provide additional reassurance that the findings with landiolol are not unexpected.

Landiolol was administered intravenously at rates between 1 and 80 mcg/kg/min in the published clinical trials and titrated to the clinical effect on HR reduction. Based on the proposed post-hoc primary composite endpoint criteria, nominally statistically and clinically significantly greater proportions of patients with SVT, including AF and AFL, treated with landiolol had decreased HR compared to placebo.

Based on the submitted placebo-controlled publications, between 42% and 89% of subjects treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 0-11% of subjects achieved the post-hoc primary endpoint of HR reduction with placebo.

Compared to active control, 43% of subjects with heart failure (HF) treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 12% of subjects achieved the endpoint with digoxin treatment. Thus, the effectiveness of landiolol was similar in patients with and without HF.

The literature did not report a dose-response relationship in the proportion of subjects with a HR reduction. The proposal to label the lower range of tested doses, specifically intravenous infusions of 10 to 40 mcg/kg/min for patients without HF, and 1 to (b) (4) mcg/kg/min for patients with HF, is concordant with the available data for effectiveness.

The treatment effect was empirically durable during continuous infusion from 5 minutes up to 24 hours and appeared to persist for approximately 30 minutes post discontinuation in most patients.

Regarding safety as evaluated from the submitted literature, a total of 1044 subjects were exposed to landiolol (45 healthy volunteers, 568 from controlled trials supporting the proposed indication, 20 from other trials supporting the proposed indication, and 411 from controlled trials not supporting the proposed indication). There was a total of 752 subjects on placebo and 143 subjects on active comparator (diltiazem and digoxin) from the comparative arms of the submitted published literature. The overall adverse event frequencies between landiolol and placebo were similar. However, an imbalance against landiolol vs. placebo was evident for hypotension. The overall frequencies of hypotension adverse events based on the system organ class preferred term for placebo-controlled trials was 6.1% in the landiolol arms vs. 1.4% in the placebo arms. These numbers were impacted by the heterogeneous nature of adverse event descriptions and definitions. A sensitivity analysis was performed that incorporated all events defined as hypotension, either by published report alone or having met a blood pressure reduction cutoff (90/50 mmHg). Based on this, the frequencies of hypotension in the landiolol arms vs. the control arms were 11% (n=63/233) vs. < 1% (n=25/540), respectively. Hypotension was the most common adverse event (expected for this class of drug). There was no adverse event relationship with dose.

There was an imbalance favoring landiolol vs. placebo for cardiovascular disorders (2.3% vs 6.0%).

In summary, based on published literature from 6 randomized placebo-controlled trials and 1 randomized active-controlled trial submitted by the Applicant, landiolol hydrochloride is effective at decreasing HR for patients with SVT, AF and AFL, including patients with a diagnosis of HF. There were no safety concerns.

CDER Cross Discipline Team Leader Review
Fred Senatore MD, PhD, FACC
NDA 217202- Landiolol Hydrochloride

CMC Review

The CMC review, written by Daniel Jansen, PhD (drug substance), Dan Berger, PhD (drug product and labeling), Allison Aldridge, PhD (manufacturing), and Joan Zhao, PhD (biopharmaceutics), supervised by Ted Carver, PhD, identified issues that precipitated a recommendation for a CR. The key issue was (b) (4), a carcinogenic substance, at (b) (4) ppb (based on landiolol quantity in the drug product) in 3 drug product batches stored for 15-16 months. These levels were not considered acceptable as they exceed the Agency-specified active ingredient (AI) of (b) (4) ng/day for (b) (4) at the 2,668 mg maximum dose. (b) (4) levels will require control to no more than (b) (4) ppb to meet the accepted AI of (b) (4) ng/day. The current (b) (4) level was judged to pose significant risks to patient safety.

Another issue was the Applicant's proposal to (b) (4) to facilitate meeting the requirements of the (b) (4) specification.

The two itemized issues were the basis of the CR recommendation. Resolution of these CR issues require the following:

Product Quality

- To ensure that the (b) (4) acceptable intake of (b) (4) ng/day is not exceeded, the Applicant is required to control (b) (4) levels to ≤ (b) (4) ppb of landiolol in the drug product throughout shelf-life.
- Include test methods and acceptance criteria for (b) (4) levels in the drug product release and stability specification.
- A (b) (4) range of (b) (4) mg API /vial will be acceptable for the drug product based on an assay specification of (b) (4) %.

Manufacturing

- (b) (4)

Pediatric Study Plan

The division agreed with the Applicant's Agreed Initial Pediatric Study Plan (iPSP), as documented in the 16 NOV 2017, letter to the Applicant. The Applicant and the Division agreed to the following plan:

- Performance of one pediatric trial (study design approved by EMA) in Europe; no separate US pediatric trial (b) (4) .
- Deferral of the trial until after NDA and subsequent approval for the adult population. There is no age-specific waiver.
- (b) (4)

Propriety Name Review

The EU trade name is RAPIBLOC®. The applicant's proposed US tradename, (b) (4), was found unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) because of potential confusion with (b) (4). If the applicant wishes to have a tradename, they will need to submit a new proposal for review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FORTUNATO F SENATORE
05/31/2023 09:13:49 AM

NORMAN L STOCKBRIDGE
05/31/2023 10:10:18 AM

HYLTON V JOFFE
05/31/2023 01:37:01 PM
This memorandum serves as the decisional memorandum on the application.