CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209964Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: **APPROVAL WITH PMC**

NDA 209964 Resub 14
Review #01

Drug Name/Dosage Form	Ivabradine Solution
Strength	5 mg/5 mL (1 mg/mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Amgen Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission (SD 1)	25-OCT-2018	*Amendment (SD 17)*	07-FEB-2019
Amendment (SD 9)	18-DEC-2018	*Amendment (SD 19)*	12-FEB-2019
Amendment (SD 10)	21-DEC-2018	*Amendment (SD 25)*	27-FEB-2019
Amendment (SD 12)	04-JAN-2019	*Amendment (SD 22)*	29-MAR-2019
Amendment (SD 14)	15-JAN-2019	*Amendment (SD 23)*	02-APR-2019
Amendment (SD 15)	18-JAN-2019	*Amendment (SD 24)*	04-APR-2019

Product Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rao Kambhampati	Wendy Wilson-Lee	ONDP
Drug Product			
Labeling			
Environmental			
Manufacturing	Mark Johnson	Rapti Madurawe	OPF
Microbiology	Wendy Tan	Bryan Riley	
Biopharmaceutics	Qi Zhang	Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

None.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	206143	Ivabradine Tablets

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL WITH PMC** of Ivabradine Oral Solution 1 mg/mL.

II. Summary of Quality Assessments

A. Product Overview

Amgen seeks approval of ivabradine oral solution for the treatment of pediatric heart failure. Ivabradine was approved as an immediate-release tablet under NDA 206143 (April 2015) to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction. In response to a FDA written request (April 2015), the applicant developed a pediatric formulation for ivabradine. Ivabradine was granted orphan designation (March 2016) for the treatment of pediatric patients with dilated cardiomyopathy.

The drug product is a simple formulation containing a (b) (4) and water as excipients. Due to potential sensitivities of pediatric patients to preservatives, the applicant chose to sterilize the drug product. The container closure is single use ampoules. The proposed administration instructions call for the caregiver to empty the contents of the ampule into a dosing cup and withdraw the appropriate amount of solution from the dosing cup using an oral syringe. The appropriate product strength and volume of solution to be administered is age and weight based.

Critical review issues for the OPQ team included: 1) sterility assurance, 2) appropriateness of the product design, including the container closure system, and formulation for the intended population, 3) formulation, design, and process attributes to mitigate potential risks associated with known degradation pathways (acidic, alkaline, photolytic, and thermal), and 4) dosing accuracy, especially in the context of multistep administration instructions.

Proposed Indication(s) including Intended Patient Population	***Treatment of pediatric heart failure***
Duration of Treatment	***Chronic***
Maximum Daily Dose (proposed)	***15 mg***
Alternative Methods of Administration	***None***

B. Quality Assessment Overview

Notable Product Quality Review Issues

Issue #1 – (b) (4) *Control Strategy*

(b) (4)

The proposed product offers a more convenient dosage form to facilitate administration of ivabradine to pediatric patients 6 months and older. The approved product is a tablet and requires manipulation prior to dosing if administered to patients in the younger pediatric age range. The oral solution is considered an advance in the treatment of pediatric heart failure. As such, OPQ considers the applicant's root cause analysis and subsequent corrective action (b) (4) sufficient to support approval of the NDA. Based on the preliminary finding that the new corrective action (b) (4) (b) (4) (b) (4) OPQ will not include information (b) (4) in Section 11 of the prescribing information. This is in keeping with current OPQ policy to only include in Section 11 ingredients intentionally added to the product such as the active ingredients and excipients.

OPQ and the applicant agreed to a product quality related post-marketing commitment provide confirmatory data (b) (4) (b) (4) (b) (4) **(PMC # 3597 Confirmation of** (b) (4) **Content in Ivabradine Oral Solution).** As part of the PMC, the applicant agrees to provide (b) (4)

(b) (4)

The (b) (4) impurity issue and proposed risk mitigation strategy was discussed as part of the Pediatric Review Committee (PeRC) meeting on April 3, 2019. The PeRC agreed that evaluation of risk and proposed risk mitigation strategy, including the OPQ PMC, were sufficient to address the safety concern and ensure safe use of the drug product in the target pediatric population.

Issue #2 – Assignment of Drug Product Expiration Date

The primary review assessment of stability data recommended a reduction in the proposed drug product expiration date based on the absence of statistical analysis of the data. This information was not requested during the review cycle to address this concern. However, given that the data for the drug product primary stability batches did not show any significant changes in any of the monitored (i.e. description, assay, impurities, pH, density, nominal volume, uniformity of dosage, sterility, (b) (4) in the intended commercial packaging, statistical analysis is not needed as noted in ICH Q1E Evaluation of Stability Data. **As such, the proposed 36-month drug product expiration date is accepted based on the 24 months long-term stability data for the primary registration batches when the drug product ampules are stored in the (b) (4) foil pouches at USP Controlled Room Temperature, protected from light.**

(b) (4)

(b) (4)

Issue #3 – Sterility Assurance

OPQ recommended a refuse to file action for the original submission based on the lack of sterilization validation information in the original submission (Refuse to File letter 16FEB2017). Although not required for oral solution, the applicant chose to develop a sterile, preservative free formulation given the known sensitivities of pediatric patients to preservatives. In the resubmission, the applicant provided all required sterilization validation information. Based on the review by the OPQ Division of Microbiology Assessment, the manufacturing process is validated with respect to sterility assurance and the proposed packaging provides sufficient protection from microbial contamination during storage.

Issue #4 – Drug Product (b) (4)

The applicant filed the resubmission with a proposal to market (b) (4) 1 mg/mL (b) (4). (b) (4) The applicant (b) (4) (b) (4) agreed that (b) (4) the 1 mg/mL strength would be marketed. (b) (4) The data submitted for the (b) (4) is still important to support the assignment of drug product expiration date based on the bracketing scheme used for the stability study. This data is also supportive of the clinical development program as well as provides additional evidence for the suitability of the drug product for marketing.

Summary of Quality Assessments (adapted from discipline review chapters)

The Applicant references NDA 206143 for all drug substance CMC information. The proposed drug product is a sterile, colorless, oral solution of ivabradine hydrochloride, maltitol, and Water for Injection. (b) (4) No preservatives are used. Maltitol had been used in other approved pediatric oral dosage formulations before. Both maltitol and WFI are of compendial grade. Compatibility of the drug substance with excipients was demonstrated by stability studies. Compatibility of the drug product solution with commonly used dosing cups and syringes was demonstrated. It was shown that the drug product solution is stable for at least two hours in the dosing components. Proposed drug product specification contained all the required tests and the proposed limits are reasonable. Batch analysis results were provided for developmental, primary stability, PPQ, and proposed commercial lots. No new impurities/degradation products were observed in the drug product at release or during

stability storage. The proposed container closure system complies with USP and regulations. **The claim for categorical exclusion is deemed acceptable in accordance with 21 CFR 25.31(b) and 25.15(d).**

The manufacturing process for commercial production of Ivabradine Oral Solution utilizes (b) (4) (b) (4) (b) (4) The overall control strategy is therefore adequate to ensure consistent production of finished product capable of meeting pre-determined acceptance criteria. **Supporting manufacturing facilities have been assessed and are acceptable for their respective intended operations based on inspectional history and demonstrated manufacturing, packaging, and testing capability.**

Sterilization of the oral solution is achieved via (b) (4) (b) (4)

This Biopharmaceutics review focused on the evaluation of the bridging between the proposed commercial oral solution vs. oral solution used in pediatric clinical studies. Dissolution test is not applicable for this dosage form (oral solution).

- The formulation used in the phase 2/3 clinical study is reported to be the same as that of the proposed commercial pediatric formulation (b) (4) .

(b) (4)

- The phase 1 comparative BA study PKH-086 is reported to demonstrate the bioequivalence between the ivabradine pediatric formulation (1 mg/mL) and the ivabradine market tablet formulation.

- The manufacturing process and site are different between the clinical and commercial product, however, no additional bridging to support changes in the process and site is needed for the proposed oral solution dosage form, from a Biopharmaceutics perspective.

Based on all the information, we determined that the Applicant's biowaiver request per 21 CFR 320.22(c)(2)(iii) is not needed. The bridging between the proposed drug product and those used in the clinical studies has been established, based on 21 CFR 320.24(b)(6). There are adequate in vivo PK and clinical data within the NDA to support the proposed commercial pediatric formulation (b) (4). Refer to the Clinical Pharmacology Review for and the Clinical Review for further details regarding the PK and clinical studies.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment	
Critical Quality Attributes	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	**Low**	(b) (4)	**Low**	
Physical Stability	**Low**		**Low**	
Dosing Accuracy	**Medium**		**Low**	
Microbiological Quality	**Low**		**Low**	
Palatability	**Medium**		**Low**	
Leachables	**Medium**			
(b) (4)	**Low**		**Low**	
pH	**Low**		**Low**	
Density	**Low**		**Low**	
Content Uniformity	**Low**		**Low**	

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NDA: 209964-Orig-1-Resub-14
Submission Type: 505(b)(1) – Type 3 New Dosage
Drug Product Name/Strength: Corlanor® (ivabradine) oral solution, (b) (4) 1 mg/mL
Applicant Name: Amgen
Dosage Form: Oral solution
Route of Administration: Oral (recommended dose: twice daily according to weight and age)
Intended for Use: Treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months to less than 18 years, who are in sinus rhythm with elevated heart rate (b) (4).
Cross Referenced NDAs:
Corlanor® (ivabradine) tablets, 5 mg and 7.5 mg, NDA 206143, approved 2015; Amgen
Primary Reviewer: Qi Zhang, Ph.D.
Secondary Reviewer: Jing Li, Ph.D.

REVIEW SUMMARY

The Applicant is seeking approval of marketing of a pediatric formulation for Corlanor® (ivabradine) tablets (NDA 206143; approved in 2015) under the 505 (b)(1) path. The proposed pediatric drug product is formulated as 5 mL single-use oral solution (b) (4) 1.0 mg/mL of ivabradine free base (b) (4) with (b) (4) mg/mL maltitol (b) (4) in Water for Injection for oral administration. The clinical studies in support of this NDA for treatment of heart failure in pediatric patients 6 months-18 years of age include a phase 2/3 efficacy and safety study (CL2-090) in pediatric subjects with DCM, a phase 1 study (PKH-086) for the relative bioavailability of ivabradine oral solution compared with tablets, and a phase 1 trial (PKE-005) that established the suitability of a dried blood spot (DBS) sampling method that was used for pharmacokinetics assessments in Study CL2-090.

This Biopharmaceutics review focused on the evaluation of the bridging between the proposed commercial oral solution vs. oral solution used in pediatric clinical studies. Dissolution test is not applicable for this dosage form (oral solution).

- The formulation used in the phase 2/3 clinical study is reported to be the same as that of the proposed commercial pediatric formulation (b) (4).
- (b) (4)
- The phase 1 comparative BA study PKH-086 is reported to demonstrate the bioequivalence between the ivabradine pediatric formulation (1 mg/mL) and the ivabradine market tablet formulation.
- The manufacturing process and site are different between the clinical and commercial product, however, no additional bridging to support changes in the process and site is needed for the proposed oral solution dosage form, from a Biopharmaceutics perspective.

Based on all the information, we determined that the Applicant's biowaiver request per 21 CFR 320.22(c)(2)(iii) is not needed. The bridging between the proposed drug product and those used in the clinical studies has been established, based on 21 CFR 320.24(b)(6). There are adequate in vivo PK and clinical data within the NDA to support the proposed commercial pediatric formulation (b) (4). Refer to the Clinical Pharmacology Review for and the Clinical Review for further details regarding the PK and clinical studies.

It is noted that, per the Applicant the BCS Class 1 classification was determined in NDA 206143 in registration of Corlanor (ivabradine) tablets. However, based on the current FDA's BCS database, Ivabradine was not classified as BCS Class I drug, because the permeability was not conclusively demonstrated, and the absolute BA is 40% (likely due to extensive intestinal and hepatic first-pass metabolism; refer to the approved US package insert for Corlanor (ivabradine) tablets, 5 mg and 7.5 mg, NDA 206143). Reference is also made to the Biopharmaceutics Review dated November 19, 2014 in DARRTS for NDA 206143 (Reviewer: Dr. Sandra Suarez).

BIOPHARMACEUTICS REVIEW RECOMMENDATION:

From the Biopharmaceutics perspective, 209964-Orig-1-Resub-14 for Corlanor® (ivabradine) oral solution, (b) (4) 1 mg/mL is **ADEQUATE** and recommended for **APPROVAL**.

Qi Zhang

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Date: 3/18/2019 03:03:59PM
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Jing Li

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background

NDA: 209964

Drug Product Name / Strength: Corlanor® (Ivabradine), (b) (4) 1.0 mg/mL for pediatric aged 6 months – 18 years

Route of Administration: Oral solution

Applicant Name: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): *N/A*

Review Summary:
- The submission is **recommended** for approval on the basis of sterility assurance.
- The product is (b) (4). There are currently no deficiencies identified based on the information provided in the submission documents.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
10/25/2018	10/25/2018	N/A	11/9/2018
01/11/2019	01/11/2019	N/A	1/23/2019

Highlight Key Outstanding Issues from Last Cycle: N/A. This is an original application review.

Remarks: This is a 505(b)(1) submission for pediatric patients ages 6 months to 18 years. The applicant reference NDA 206143 for the adult dosages for any regulatory documents as needed. The applicant applied for and has been granted priority review for Orphan Drug Designation.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: None

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Reviewer's Assessment: ***Adequate***

The method suitability validation data from both (b) (4) and (b) (4) indicated that the drug product is not bacteriostatic or fungistatic and can be used for routine tests.

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: ***Please refer to P.1***

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(P.8.1)

Proposed Expiry: 36 months
The data provided indicated that the drug product is "sterile" when stored at 25C for up to 24 months, based on the stability data provided in the submission.

Reviewer's Assessment: ***Adequate***

Stability study data up to 24 months stored at the long-term storage conditions is provided by the applicant to justify the proposed 36 months shelf life.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(P.8.2)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	Meets USP <71>

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25° ± 2°C/60% ± 5%RH

Test	Time (Months)			
	0	12	24	36
Sterility	X	X	X	X

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: ***Adequate***

The stability protocol and commitment provided is within regulatory expectation.

P.8.3 Stability Data

Stability data are provided long-term storage conditions for 2 strengths of the drug product.

25±2°C/ 40% ± 5% RH;
Sterility – Meets USP <71>
Tested at initial, 3M, 6M, 9M, 12M, and 24M ((b) (4) 1.0 mg/mL)

Reviewer's Assessment: ***Adequate***

R Regional Information

Executed Batch Records

Executed lot #(s): 1092420, 1092421, 2092422, 1092423, 1092424

The batch records confirm that the Executed Batches 1092420, 1092421, 2092422, 1092423, 1092424 were produced using validated (b) (4) manufacturing processes. The records indicated that (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

Comparability Protocols

R.2 Comparability Protocol – N/A

Reviewer's Assessment: ***N/A***

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

PACKAGE INSERT
(1.14.1.3 package insert)

Storage temperature: 20°-25°C (68° to 77°F), excursion permitted to 15-30°C
Route of administration: Oral solution
Container: Single-use ampule

Reconstituted/Further Diluted Drug Product
The product is formulated as ready-to-use solution. No reconstitution or further dilution is required. Package insert label includes instruction to discard remaining solution immediately after use.

Reviewer's Assessment: ***Adequate***

The information provided in the package insert is acceptable for the dosage form preparation and administration instruction.

Post-Approval Commitments:

Reviewer's Assessment: ***N/A***

List of Deficiencies:

There are currently no deficiencies identified based on the information submitted.

Primary Microbiology Reviewer Name and Date:
Wendy Tan, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
February 1, 2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Bryan S. Riley, Ph.D.
Branch Chief
CDER/OPQ/OPF/DMA/BII
February 1, 2019

Bryan Riley

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Wilson- Lee

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