CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206143Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 206143
Drug: Corlanor (ivabradine) 5 mg & 7.5 mg Tablets
Class: a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker
Sponsor: Amgen, Inc
Indication: Proposed: to reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4)

Final indication: reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Date of submission: June 27, 2014
PDUFA date: February 27, 2015 (original), May 27, 2015 (Major amendment)
Action date: April 15, 2015

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross Discipline Team Leader (CDTL)
    - Thomas Marciniak
  - Medical Reviewer
    - Preston Dunnmon (Efficacy), Nhi Beasley (Safety)
  - Pharmacology & Toxicology
    - Jean Wu
  - Regulatory Health Project Manager
    - Alexis Childers
- Office of New Drug Quality Assessment (ONDQA), Branch I
  - – CMC & Biopharmaceutics
    - Wendy Wilson (DS), Pei-I Chu (DP)
    - Sandra Suarez (Biopharm)
- Office of Clinical Pharmacology
    - Martina Sahre (clinpharm)
    - Sreedharan Sabarinath (pharmacometrics)
- Office of Biostatistics, Division of Biometrics I
    - Steve Bai
- Office of Surveillance and Epidemiology
  - – DMEPA
    - Janine Stewart
  - DRISK

- Danny Gonzalez

❖ BACKGROUND

Ivabradine, developed by Les Laboratoires Servier, slows heart rate by modulating pacemaker activity in the sinus node. ivabradine is a first in class for HCN (hyperpolarization activated cyclic nucleotide-dated) channel blocker. It is currently marketed in 64 countries for the treatment of chronic heart failure and in 100 countries for the treatment of angina. Amgen recently acquired the commercial rights for the USA.

There is not an active IND. Prior to submission there was a Pre-NDA and Top-Line Results meeting with Amgen to discuss the submission.

The clinical development of ivabradine consisted of 5 Phase 2 studies in chronic heart failure, a single large, randomized, placebo-controlled outcomes study entitled Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial (SHIFT). The SHIFT data will provide the primary support for the safety and efficacy of ivabradine for this indication. BEAUTIFUL, a phase 3 international, multicenter, randomized, double-blind, parallel group, placebo-controlled, long –term outcomes study assessing the effects of ivabradine on mortality and cardiovascular events in patients with stable CAD and left ventricular systolic dysfunction will provide supportive information. In addition, several studies have been conducted in patients with stable angina pectoris.

The NDA was given a priority review with a PDUFA date of February 27, 2015. During the LCM meeting it was determined that data from SIGNIFY should be reviewed and was classified as a major amendment. The new PDUFA date was set as May 27, 2015. Upon reviewing data further, it was determined that SIGNIFY data is supportive and the patient population was different enough than the intended population for which the NDA was submitted. It was also determined that an Advisory Committee meeting was not needed.

The proposed doses are 5 and 7.5 mg for the treatment of heart failure.

The review of the application in general met all of the 21st century review guidelines except for labeling negotiations. The sponsor was notified in advance.

User Fee

The user fee for this application was paid in full on April 11, 2014. User Fee ID (b) (4).

Pediatric Review Committee (PeRC)

The sponsor submitted a waiver request in Pediatrics. The PeRC meeting to discuss this application was held on 3 September 2014. The committee agreed to grant a full waiver in pediatric patients because studies are impossible or highly impractical as there are too few patients with disease/condition to study.

Advisory Committee

There was no Advisory Committee meeting for this NDA because this drug does not raise significant safety or efficacy issues.

Trade name

The sponsor originally submitted the proposed name CORLANOR on 26 September 2013 but withdrew the request on 2 October 2013 at the request of DMEPA stating the request cannot be submitted until there is an active application. The sponsor subsequently resubmitted the request on 27 June 2014. A review was completed on 23 September 2014 with a grant letter issued on 23 September 2014.
The sponsor revised the container labels per DMEPA's recommendations. DMEPA found them acceptable.

Facilities Inspection
The Office of Compliance provided an overall recommendation of acceptability for the manufacturing sites on 19 December 2014.

Division of Scientific Investigations: Five foreign clinical investigator inspections were conducted in support of NDA 206143, for audit of Protocol CL3-16257-063 (SHIFT study). No regulatory violations were found during 2 of the inspections. Minor regulatory violations were found during the inspections of 3 of the sites for failure to follow the investigational plan. These issues did not significantly impact the quality or the integrity of the data submitted in support of this NDA.

❖ REGULATORY TIMELINE

- Top-Line Results Meeting: 22 Jan 2014 (minutes dated 20 Feb 2014)
- Pre-NDA Meeting: 23 Jan 2014 (minutes dated 18 Feb 2014)
- CMC Pre-NDA : 6 Dec 2013 (minutes dated 23 Dec 2013)
- NDA Received Date: 27 Jun 2014
- Filing Meeting: 4 Aug 2014
- Filing/74 Day Letter: 25 Aug 2014
- Mid-cycle Communication Meeting: 6 Oct 2014 (minutes dated 21 Oct 2014)
- Late-Cycle Meeting: 9 Jan 2015
- Advisory Committee: N/A
- PDUFA Date: 27 May 2015

❖ REVIEWS

Below are the conclusions reached by the Corlanor team members, organized by role or discipline.

ODE I Memorandum (dated 15 Apr 2015)
Dr. Unger provided a thorough review providing his summary and assessment of each discipline's review. He also discussed analyses he conducted to draw his conclusions. He explains that there was a difference in how the Division and the sponsor conducted analyses. He agrees with Dr. Stockbridge's assessment and conclusions regarding little interaction with loop diuretics as Dr. Marciniak's review suggests. Dr. Unger shares the teams concerns regarding the applicability of SHIFT results to US patients, especially regarding the underuse of CRT and ICDs.

Dr. Unger does not believe there is a strong effect on mortality. When the primary composite endpoint of SHIFT is destructed, the treatment effect was driven entirely by hospitalizations for worsening heart failure, see full review for explanation. He notes the inconsistencies with the other 2 trials on mortality as well. He does not feel that mortality should be part of the indication statement but should be mentioned in section 14 of the label. Amgen agreed.

Overall, Dr. Unger agrees with the review team's recommendation for approval.

Divisional Memorandum (dated 4 Mar 2015)
Dr. Stockbridge's memo recommends an approval. The memo provides a summary of the reviewer's major findings as well as his opinion on study findings.

While reviewers felt that SHIFT, BEAUTIFUL and SIGNIFY all had inconsistencies, Dr. Stockbridge feels the patient populations were different enough to not find the results inconsistent or difficult to interpret. He finds the interactions by heart rate and beta blockers plausible, but he says there is a possibility this is spurious. Regarding the interactions with loop diuretics, he believes the findings are not credible.

Dr. Stockbridge believes that the findings in SHIFT reduce the combined risk of CV death and hospitalization for worsening heart failure. He feels the indication should reflect this and not be restricted just to hospitalization.

Deputy Director memo (dated 24 Mar 2015)
Although not part of the review team, Dr. Grant provided an assessment on the label's proposed indication statement (b) (4). He believes the statement does not accurately convey the benefit of ivabradine. Dr. Grant believes that the effect on the primary endpoint was only based on the result of a reduction in hospitalization for WHF.

Cross-Discipline Team Leader (CDTL) Review (dated 8 Dec 2014)
Dr Marciniak recommends approval although he is not in total agreement with the reviewer's opinion for an indication. His review provides a summary of each disciplines recommendations and major findings as well as providing his own assessment of each review.

Dr. Marciniak's provided 3 additional reviews in addition to the CDTL memo. The reviews summarize what he believes were major issues for approval. These include inconsistency between 3 trials and subgroup interpretations. Based on his analyses, he concludes that ivabradine has beneficial effects when used concomitantly with loop diuretics but is deleterious without loop diuretics.

Medical (dated 4 Dec 2014)
Dr's Dunnmon and Beasley provided a combined review discussing safety and efficacy. They both recommended approval. They state that the trial result was primarily driven by the hospitalization component of the primary endpoint while there was a non-significant lean towards the CV mortality component. The review also indicates that there is a nominally significant improvement on CV mortality only in a sub-population taking no-beta blockers.

They stated that bradycardia is a principle adverse event and recommend a starting dose of 2.5 mg in patients with baseline heart rates < 85 bpm. They also do not recommend a REMS.

Biostatistics Review (dated 17 Nov 2014)
Dr. Bai's review discussed the pivotal trial (SHIFT) and two cardiovascular outcome studies (BEAUTIFUL and SIGNIFY). The primary objective of SHIFT was met. There also appeared to be a lean on mortality. He explains however, that the findings of the BEAUTIFUL, and SIGNIFY trials are inconsistent with SHIFT. Both trials failed their respective primary composite endpoints, which are very similar to the primary endpoint of SHIFT. BEAUTIFUL did not demonstrate an overall treatment benefit with ivabradine. In SIGNIFY, the results were neutral with a negative lean on CV and all-cause mortality. He states that the reasons for the differences should be addressed. He did not provide a recommendation on approval.

Clinical Pharmacology Review (dated 26 Nov 2014 & 10 Apr 2015
Dr.'s Sahre (clinical pharmacology) and Sabarinath (pharmacometrics) provided a combined review. They find the information submitted to the NDA to be supportive of approval and sufficient to provide appropriate dosing instructions.
The most noteworthy findings were (for a complete list, see review):

- Ivabradine and its main metabolite S18982 are extensively metabolized with CYP3A4.
- The absolute bioavailability of ivabradine after oral administration is 40 %.
- (b) (4) levels similar to human exposures. However, an interaction study with metformin did not show an effect upon metformin exposure.
- There is an association between baseline and on-treatment heart rate reduction and incidence rate for cardiovascular death or hospitalization for worsening of heart failure for both ivabradine and placebo treatments.

- coadministration with verapamil and diltiazem should be avoided since both drugs can act as negative chronotropes.
- St. John's Wort extract should not be used and grapefruit juice should be avoided (b) (4)

They also provided an addendum explaining their reasoning why they do not agree with the sponsor's proposal for stating that the half-life of the drug is (b) (4) hours. The clinpharm reviewers recommend the half-life be documented as 6 hours. This is based on the fact that the basic PK characteristics of ivabradine should be derived from dedicated PK studies with rich sampling when available rather than the population PK model.

Pharmacology & Toxicology Review (dated 28 November 2014)
Since no studies were conducted under an IND, Dr. Wu reviewed all data under the NDA. Separate reviews were created for reproductive and developmental toxicology, carcinogenicity, and genetic toxicology. A review summarizing the aforementioned reviews was issued on 28 November 2014 and included the pharmacology/toxicology assessment.

Dr. Wu's review stated that the major organs of toxicity are the heart and eye. Myocardial lesions were seen in rats but not dogs, although treatment related ECG findings were noted in dogs. Transient visual symptoms were noted in dogs. Any genotoxic risks noted are considered minimal. Ivabradine is excreted in the milk therefore Dr. Wu is recommending a contraindication in pregnant women. Dr. Wu is providing labeling recommendations. As long as labeling is agreed upon, there are no safety issues with the use of ivabradine from a pharm/tox perspective. Dr. Wu recommends approval.

Tertiary Pharmacology Review (8 Apr 2015)
Dr. Brown summarized the pharmacologists review and agrees with Dr. Wu's assessment that the nonclinical information is adequate to support approval

Office of New Drug Quality Assessment (ONDQA), Branch I, Review (dated 2 December 2014)
A combined reviewed was created by the drug substance (Wendy Wilson) and drug product reviewers (Pei-I Chu). All drug substance analytical methods are validated and appropriate. The drug product is an immediate release film-coated, scored tablet in two strengths. Based on stability data provided a 36 month shelf life will be granted for blister packaging and 24 month shelf life for bottle packaging. The reviewers state that the CMC information provided is adequate and recommend approval.

Biopharmaceutics (21 Nov 2014)
Dr. Suarez recommends approval. The drug substance data shows that the drug substance has high solubility and the drug product dissolves rapidly.

Microbiology (6 June 2014)
Dr. Riley's review states that the microbial limits specifications are acceptable.

CONSULTS

Office of Surveillance and Epidemiology Reviews (26 Nov 2014), (2 Mar 2015)
DMEPA
Dr. Stewart reviewed that carton and container labels and labeling insert using a Failure Mode and Effects Analysis. The risk assessment performed on the PI and container labels identified deficiencies that may lead to medication errors and areas for improvement
Full detail on recommendations can be found in the review. Comments regarding the container labels were sent to the sponsor via email. Responses were found acceptable.

DRISK (3 Mar 2015)
Dr. Gonzalez evaluated the need for a risk evaluation and mitigation strategy (REMS). He concludes that any risks noted with currently available data is comparable to other drugs used for the treatment of CHF; therefore a REMS is not needed.

Office of Medical Policy Initiatives, Division of Medical Policy Programs (9 Mar 2015)
Ms. Dowdy did a combined review with Dr. Patel evaluating the Medication Guide. See full review for comments regarding the Medication Guide. They concluded that the document is acceptable pending proposed corrections.

Office of Prescription Drug Promotions, Division of Professional Drug Promotion (3 Mar 2015)
Dr. Patel provided comments on the draft prescribing information and carton container. See full review for details

Labeling
Labeling discussions occurred with the sponsor. The final agreed upon labeling will be attached to the approval letter.

CONCLUSION
The review team recommended approval.

An approval letter was created and signed by Dr. Unger on 15 April 2015.

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/s/

ALEXIS T CHILDERS
04/15/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: 6 April, 2015

From: Melissa S Tassinari, PhD, DABT
Senior Clinical Advisor
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS
Acting Team Leader, Maternal Health, DPMH

Lynne P Yao, MD
Acting Division Director,
Division of Pediatric and Maternal Health

To: Division of Cardio Renal Products (DCRP)

Drug: Corlaner (ivabradine)

NDA: 206143

Applicant: Amgen

Drug Class: Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker

Indication(s): Treatment of patients with stable, symptomatic (b) (4) chronic heart failure with reduced left ventricular function (left ventricular ejection fraction ≤ 35%), who are in sinus rhythm with resting heart rate ≥ 70 beats per minute (bpm) on maximally tolerated doses of beta blockers or contraindicated to beta blocker therapy.

Subject: Labeling under the Pregnancy and Lactation Labeling Rule (PLLR)
Consult Date: 11 February 2015

BACKGROUND

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) published the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be replaced with a narrative summary in all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format.

Ivabradine

As noted from the proposed labeling, "Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated for the treatment of patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute (bpm) and on maximally tolerated doses of beta blockers unless beta blocker use is contraindicated." Ivabradine was approved in the European Union in 2005 for the treatment of angina and heart failure (tradenames in the EU are Corlentor/Procoralan).

DCRP requested a consult on February 11, 2015, to review the labeling for pregnancy and lactation to ensure compliance with the PLLR formatting requirements and provide comments to be included in the substantially complete labeling that was sent to the applicant. A full data review was not performed by DPMH. The comments in this memorandum reflect only advice on the appropriate formatting of the existing pregnancy, lactation, and reproductive risk data as required under PLLR. DMPH attended a meeting with DCRP on February 25, 2105 to present labeling recommendations. On March 27, 2015 the revised labeling from the applicant was reviewed to assure adequate responses to original comments.

RECOMMENDATIONS

DPMH provided the following initial comments as noted in Appendix A. Comments on the revised labeling are noted in Appendix B. DPMH refers to the final NDA action for final labeling.

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/s/

MELISSA S TASSINARI
04/06/2015

TAMARA N JOHNSON
04/06/2015

LYNNE P YAO
04/08/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 9, 2015

To: Alexis Childers
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Corlanor (ivabradine) tablets
NDA: 206143
Comments on draft labeling

As requested in DCRP's consult dated August 18, 2014, OPDP has reviewed the draft prescribing information (PI) and proposed carton and container labeling for Corlanor (ivabradine) tablets.

OPDP reviewed the draft PI titled, "NDA 206143 First Version Comments to Sponsor" received via the DCRP SharePoint website on February 24, 2015. OPDP's comments are provided in the attached clean version of the draft PI.

OPDP has also reviewed the following proposed carton and container labeling submitted by Amgen Inc. on February 18, 2015:

- Carton DP Blister 5 mg and 7.5 mg 10ct Sample
- Carton DB Blister 5 mg and 7.5 mg 60ct
- Label Bottle - 5 mg 60ct, 180ct, 14ct Sample
- Label Bottle - 7.5 mg 60ct, 180ct, 14ct Sample
- (b) (4) Blister Pack 5mg 10ct Sample, 60ct
- Blister Pack 7.5 mg 10ct Sample, 60ct

OPDP notes that the graphic presented in conjunction with the tradename makes representation of the product's approved indication. Specifically, the graphic is representative of the heart, thereby rendering it promotional. OPDP recommends deleting the graphic.

Thank you for the opportunity to review the proposed PI and draft carton and container labeling. If you have any questions on the comments, please contact Zarna Patel at zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
03/09/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 9, 2015
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Britt Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Corlanor (ivabradine)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 206143
Applicant:	Amgen Inc.

1 INTRODUCTION

On June 27, 2014, Amgen Inc. submitted for the Agency's review a New Drug Application (NDA) 206143 for Corlanor (ivabradine) Tablets with the proposed indication to reduce the risk of [redacted] (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure [redacted] (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), [redacted] (b) (4) maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated [redacted] (b) (4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Cardiovascular and Renal Products (DCRP) on January 16, 2015, and August 18, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Corlanor (ivabradine) Tablets.

2 MATERIAL REVIEWED

- Draft Corlanor (ivabradine) Tablets MG received on January 16, 2015 and received by DMPP and OPDP on February 24, 2015.
- Draft Corlanor (ivabradine) Tablets Prescribing Information (PI) received on June 27, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 24, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
03/09/2015

ZARNA PATEL
03/09/2015

LASHAWN M GRIFFITHS
03/09/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	March 2, 2015
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 206143
Product Name and Strength:	Corlanor (ivabradine) Tablets, 5 mg and 7.5 mg
Submission Date:	February 18, 2015
Applicant/Sponsor Name:	Amgen Inc.
OSE RCM #:	2014-1252-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular & Renal Products (DCRP) requested that we review the revised container labeling and carton labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labeling and carton labels are acceptable from a medication error perspective.

[1] Stewart J. Label and Labeling Review for Corlanor (NDA 206143). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 NOV 26. 18 p. OSE RCM No.: 2014-1252.

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/s/

JANINE A STEWART
03/02/2015

CHI-MING TU
03/02/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 15, 2014

TO: Tom Marciniak, Medical Team Leader
Preston Dunmon, Medical Officer
Alexis Childers, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206143

APPLICANT: Amgen, Inc.

DRUG: Corlanor™ (ivabradine)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Reduction of [redacted] (b) (4) or hospitalization for worsening heart failure, in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction

PROTOCOL: # CL3-16257-063: Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction (LVSD): SHIFT study. A three-year randomized double-blind placebo controlled international multicenter study.

CONSULTATION REQUEST DATE:	August 6, 2014
INSPECTION SUMMARY GOAL DATE:	December 15, 2014
ADVISORY COMMITTEE	January 14, 2015
DIVISION ACTION GOAL DATE:	February 27, 2015
PDUFA DATE:	February 27, 2015

I. BACKGROUND:

Amgen submits NDA 206143 oral ivabradine (2.5, 5.0 or 7.5 mg BID) for the reduction of the risk of [redacted] (b) (4) hospitalization for worsening heart failure in patients with chronic heart failure [redacted] (b) (4) and in sinus rhythm with heart rate ≥ 70 bpm, [redacted] (b) (4) beta-blocker therapy or when beta-blocker therapy is contraindicated [redacted] (b) (4)

Heart failure affects more than 5 million adults in the United States (U.S.), or 2.1% of the adult population, and its prevalence is projected to increase by > 25% by 2030. Despite currently available therapy, heart failure results in approximately 56,000 deaths annually in the U.S.; U.S. patients with heart failure have 1-year and 5-year adjusted mortality rates estimated at approximately 30% and 48%, respectively.

Ivabradine is a [redacted] (b) (4) heart rate lowering agent, which modulates the activity of pacemaker cells in the sinoatrial node and thereby decreases heart rate (HR) without any negative inotropic or dromotropic effects. Ivabradine obtained a European Marketing Authorization (EU tradename: Procoralan) in October 2005, for the treatment of chronic symptomatic stable angina pectoris in patients with normal sinus rhythm who have contraindications or intolerance to beta-blockers. The indication was widened in September 2009 for use in combination with beta-blockers in patients who are inadequately controlled with an optimal beta-blocker dose and whose HR is > 60 bpm.

The clinical evaluation of efficacy for this NDA was based primarily on the results of a large, multi-center, randomized, double-blind, placebo-controlled (on top of standard-of-care therapy including maximally tolerated beta-blockers), phase 3 outcomes trial CL3-16257-63 (Systolic

Heart failure treatment with the **If** inhibitor ivabradine **T**rial, or SHIFT) The study randomized 6558 subjects (1:1 ivabradine: placebo) at 677 study centers in 37 countries outside the U.S., including Canada, Australia, and countries in Western Europe, Eastern Europe, Asia, and South America. Ivabradine was developed by Les Laboratoires Servier and as of March 2013 has been approved in 64 countries outside the U.S. for the treatment of chronic heart failure and in 100 countries for the treatment of angina. Amgen acquired U.S. commercial rights to ivabradine from Les Laboratoires Servier and submitted as an NDA with the current indication in early 2014. The SHIFT study was conducted between September 2006 and April 2010.

Design: The phase 3 pivotal study of oral ivabradine in chronic heart failure, SHIFT (NP29800), was designed as a long-term morbidity-cardiovascular mortality study with an active double-blind treatment period from 12 to 52 months (extended by Protocol Amendments 5 and 6). Randomization was stratified on beta-blocker intake (yes/no) at time of randomization. After the month 4 visit, follow-up visits were planned every four months thereafter until the end-of-study.

Primary Efficacy Endpoint: The primary composite endpoint was the time to first event among cardiovascular death (including death from unknown cause) or hospitalization for worsening heart failure. The study was event driven and designed to terminate after at least 1600 primary composite endpoints had occurred.

Reasons for Site Selection:

The following sites with relatively high enrollment were chosen for inspection. Other factors for selecting sites for clinical inspection included the following:

- Site 1352 (Macarie) had a high treatment effect size.
- Site 4313 (Gersamija) had a low numbers of SAEs reported, and a high treatment effect size.
- Site 4232 (Marchev) had a low number of SAEs reported.
- Site 1364 (Opris) had a very low number of SAEs reported.
- Site 4250 (Donova) had a low number of primary efficacy events and a low number of SAEs reported.

II. Results

Name of CI/ Site #	**Protocol #, # of Subjects enrolled**	**Inspection Dates**	**Final Classification**
Temenuga Donova, Sofia, Bulgaria Site 4250	CL3-16257-063 35 subjects	November 3 – 7, 2014	Pending: NAI

Arcil Gersamija Latvia Site 4313	CL3-16257-063 71 subjects	October 20 – 24, 2014	Pending: VAI
Cezar Macarie Bucharest, Romania Site 1352	CL3-16257-063 92 subjects	November 3 – 6, 2014	Pending: NAI
Sotir Marchev Sofia, Bulgaria Site 4232	CL3-16257-063 53 subjects	November 10 – 14, 2014	Pending: VAI
Maria Opris Romania Site 1364	CL3-16257-063 45 subjects	November 17 – 21, 2014	Pending: VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Temenuga Donova, (Site 4250)
1 St Georgi Sofiiski Str
Sofia, Bulgaria

a. What was inspected: The inspection was conducted according to Compliance Program 7348.811. Dr. Donova has three IND studies in the CDER database and no prior inspections. This site was chosen to inspect because of high enrollment, low number of endpoint events, and low number of Serious Adverse Events (SAEs) reported.

This site screened and enrolled 35 subjects. All subjects completed the study. A total of three subjects had Serious Adverse Events, including two with endpoint events.
The field investigator reviewed records for fifteen subjects, which included corroborating data listings with source records for adverse events, inclusion and exclusion criteria, laboratory values, primary efficacy endpoints, and concomitant medications. The field

investigator also established the CHF diagnosis and classification, and reviewed copies of cardiac catheterization and echocardiogram reports with ejection fraction values. Informed consent documents were reviewed for fifteen subjects.

b. General observations/commentary: The primary efficacy endpoint data was verifiable. Adverse events appeared to be documented, and there was no evidence of under-reporting of adverse events. Documentation indicated that laboratory reports were reviewed by the investigators. Significant deviations were not observed with respect to drug accountability records and informed consent documents. No FDA 483 was issued.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The final EIR for Dr Donova was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs and email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

2. Arcil Gersamija (Site 4313)
Viestura street 5
Dauga Vpils 5403
Latvia

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Gersamija has one IND in the CDER database and no prior FDA inspections. This site was selected for inspection because of high enrollment, low treatment effect size, and a low number of SAEs reported.

The site screened 72 subjects and enrolled 71 subjects into the study. A total of 54 subjects completed the study. There were 17 deaths. The first subject was screened January 22, 2007, and the last follow-up visit for any subject occurred March 26, 2010.

Records reviewed during the inspection included informed consent documents, subject medical records, progress/visit notes, electrocardiogram (ECG) tracings, laboratory records, enrollment logs, drug accountability records, temperature logs, Ethics Committee correspondence, sponsor correspondence, and delegation logs.

The field investigator reviewed inclusion and exclusion criteria and adverse events for eighteen subjects (25% of total). For eighteen subjects, she corroborated the primary endpoint events (cardiovascular death or hospitalization for worsening heart failure), and also corroborated secondary endpoints of New York Heart Association Classification (NYHA), heart rate from electrocardiogram, physician assessment, and laboratory results. A data audit of hospitalization for any cause and for cardiovascular reason was conducted. Serious Adverse Events (SAEs) for eight subjects were reviewed.

b. General observations/commentary:

For the eighteen subject records reviewed, the data listings corroborated with source records with respect to the primary and secondary efficacy endpoints, and for adverse events. In general, the clinical investigator followed the protocol with respect to enrollment of subjects, randomization procedures, administration of study drug, and protocol required procedures.

There were a few minor deficiencies that were discussed with Dr. Gersamija at the conclusion of the inspection. The investigator found that source documentation was incomplete in some cases and that several additions or changes to progress notes did not include the date or initials of the person making the change. These were sporadic and minor and unlikely to impact the integrity of the data from this site.

The protocol required that the ejection fraction (EF) of ≤ 35% be measured within the previous three months while the subject was in 'stable' condition. There was one instance of a subject (#4368) who was hospitalized on (b) (6) with complaints of shortness of breath, edema, dull chest pain after exertion, dry throat and weakness. The patient received an echocardiogram on the same day of hospitalization and was enrolled in the study with ejection fraction of 33%. Although the ejection fraction qualified the subject for enrollment, the echocardiogram was taken during a time when the patient was hospitalized with complaints, and not necessarily in stable condition. This protocol deviation was not included in the data listings. During the close-out visit, Dr. Gersamija provided a copy of this patient's echocardiogram on September 27, 2007 where he had an EF of 34%. Dr. Gersamija explained that at the time of treatment the patient's dyspnea had stopped, and he saw little difference between the echocardiogram that was done on September 27, 2007 and the one done on (b) (6), which is why he considered the patient in stable medical condition, and enrolled the subject into the study. This item was discussed with Dr. Gersamija at the conclusion of the inspection.

At the conclusion of the inspection a one- observational, FDA Form-483 was issued for failure to follow the investigational plan. The protocol required that for serious adverse events the sponsor must be notified immediately. The field investigator identified four subjects who experienced Serious Adverse Events (SAEs) that were not reported to the sponsor immediately. For example:

1. Subject 0074 experienced occlusion of the right femoral artery with critical ischemia of the right foot on (b) (6), and ischemic stroke on (b) (6). The site became aware of these events on February 23, 2009, and reported them to the sponsor on March 14, 2009, 19 days later.
2. Subject 1016 experienced a myocardial infarction on (b) (6). The site became aware of the event on July 19, 2008 and reported to the sponsor on August 3, 2008, fifteen days later.

3. Subject 3032 had an ischemic stroke on (b) (6). The site became aware of the event on September 21, 2008, and reported the SAE to the sponsor on September 30, 2008, eight days later.
4. Subject 0129 had sudden death on (b) (6). The site learned of the event on October 26, 2007 and reported the event to the sponsor on October 30, 2007, four days later.

Dr. Gersamija responded to the FDA 483 observational findings, by letter dated November 12. He stated the reason for the delay in reporting of SAEs was because he tried to collect additional data and documents. He also provided a corrective action plan to prevent this from occurring in future studies.

c. Assessment of data integrity: In general, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The final EIR for Dr Gersamija was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs and email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

3. Cezar Macarie (Site 1352)
Sos. Fundeni 258, Sect 2
Bucharest 22328
Romania

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Macarie has seven IND studies in the CDER database and a prior inspection conducted in July 2008 was classified as VAI for failure to follow the investigational plan. This site was chosen to inspect because it was the highest enrolling site, with a high treatment effect size.

This site screened 106 subjects and enrolled 92 subjects. The field investigator reviewed 21 subject records (23% of enrolled subjects) during the inspection.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA-483 was issued. The inspection was classified as NAI. There was no evidence of under-reporting of adverse events, and the primary efficacy data was verifiable.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Macarie was not available at the time this clinical inspection summary was written. The observations noted are based on email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

4. Sotir Marchev (Site 4232)
67A, Stoletov Blvd.
Sofia, Bulgaria

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Marchev has five INDs in the CDER database and no prior inspections. This site was chosen to inspect because of a low number of SAEs reported.

Site representatives indicated that Dr. Marchev was no longer associated with the study site hospital, and had moved his operations to another medical center in Bulgaria. Dr. (b) (6) was a sub-investigator on the trial and represented the study site during the inspection.

This site screened and enrolled 53 subjects, and enrolled 53 subjects. All subjects completed the study. The field investigator reviewed twelve subject records. These records included review of inclusion and exclusion criteria to ensure subjects met eligibility criteria, concomitant medications, documentation of the subject's prior hospitalizations for relevant events and establishing the CHF diagnosis, and copies of early cardiac catheterization reports and echocardiography reports with ejection fraction values.

The field investigator also reviewed the site monitoring log and site visit feedback letters from monitors. Drug accountability records were reviewed.

b. General observations/commentary: The primary efficacy endpoint data was verifiable. Adverse events were documented, and there was no evidence of under-reporting of adverse events. Serious adverse events including deaths were consistent with data listings. Documentation indicated that laboratory reports were reviewed by investigators. No significant deviations were observed.

At the conclusion of the inspection, a one observational Form FDA- 483 was issued for not performing an investigation in accordance with the signed statement of investigator and investigational plan. To summarize, heart rate data was inconsistently entered for one subject; a beta-blocker medication data was inconsistently entered for another subject potentially affecting the randomization scheme; and a third subject was treated with an excluded concomitant medication while receiving study medication, and not withdrawn from the study. Specifically:

1. For Subject #2345 the registration and dispensing 16-Month visit worksheet dated March 31, 2009, and confirmation from IVRS indicated that the subject's heart rate was 88 beats per minute (bpm). The initial entry into the e-CRF made by Dr. (b) (6) on May 17, 2009 was 88 bpm. The subject's ECG dated March 31, 2009 documented a heart rate of 94 bpm, and on June 17, 2009, Dr. (b) (6) corrected the heart rate to 96 in the e-CRF. The adverse event of high heart rate was resolved at the

Month 20 visit on July 16, 2009, and the dose of medication increased to 7.5 mg.

2. Records indicated that Subject #3681 was enrolled on February 14, 2008, and received clarithromycin, an excluded concomitant medication, between February 17, 2009 and March 4, 2009. The protocol states that if treatment with a strong CYP3A4 inhibitor (e.g. clarithromycin) is required, administration of the study drug should be stopped.

3. The randomization records for Subject #4306 indicated that this subject was not receiving a beta-blocker when randomized on April 14, 2008. The randomization confirmation report states the subject was receiving a beta-blocker at inclusion. Review of the subject's medical history notes with a translator did not reveal a reference to a beta- blocker medication at randomization.

The above deficiencies are minor and unlikely to importantly impact the integrity of the data at this site. Dr. Marchev responded by letter dated November 24, 2014 to the FDA 483 inspectional observations. His letter promised corrective action, and is acceptable.

d. Assessment of data integrity: Although the above deficiencies were observed concerning not following the investigational plan, they are unlikely to significantly impact the integrity of the data submitted. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Marchev was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs and email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

5. Maria Opris (Site 1364)
Gh. Marinescu str. 50
Tg. Mures 540136
Romania

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Opris has no INDs listed in CDER's COMIS database and no prior FDA inspections. This site was chosen to inspect because of high enrollment and low number of SAEs reported.

This site screened 50 subjects and enrolled 45 subjects. A total of 44 subjects completed the study. The field investigator reviewed records of fourteen subjects. For these subject records, the field investigator corroborated the data listings with source documentation with respect to adverse events, including serious adverse events, deaths, inclusion and exclusion criteria, concomitant medications, CHF diagnosis, primary efficacy events. He also reviewed the randomization printouts,

electrocardiogram (ECG) tracings, the monitoring log, correspondences from the sponsor, IRB and CROs, and drug accountability records.

b. General observations/commentary: At the conclusion of the inspection a one-observational Form FDA- 483 was issued for an investigation not conducted in accordance with the investigational plan. Specifically, for subject records reviewed, the field investigator observed that two subjects who were taking an excluded medication (diltiazem) were enrolled into the study.

1. Subject 01075: subject records including the CRF indicated that the subject had begun taking the excluded medication diltiazem on April 13, 2007 and continued through completion of the study. The subject was randomized on June 28, 2007 and completed the study on or about July 14, 2008.

2. Subject 00465: subject records including the CRF indicated that this subject had begun taking the excluded medication diltiazem on March 15, 2007 and continued through completion of the study. The subject was randomized on April 27, 2007 and completed the study on or about March 23, 2010.

Dr. Opris responded by letter dated December 2, 2014, to the FDA 483 inspectional observations. Dr. Opris stated that treatment with diltiazem to both patients was prescribed by the previous cardiologist as they had contraindicated to the beta blockers because of pulmonary hypertension and peripheral artery disease. Diltiazem was contraindicated by the protocol, and unless a waiver was obtained, should not have been used. The above deficiencies were reported as protocol violations to the sponsor.

The above deficiencies are unlikely to significantly impact the integrity of the data from this site in support of the indication.

c. Assessment of data integrity: The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

Note: The final EIR for Dr. Opris was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five foreign clinical investigator inspections were conducted in support of NDA 206143, for audit of Protocol CL3-16257-063 (SHIFT study). No regulatory violations were found during the inspections of Drs. Donova (Site #4250) and Macarie (Site #1352). These inspections were classified as NAI. Minor regulatory violations were found during the inspections of Dr. Gersamija (Site #4313), Marchev (Site #4232), and Opris (Site #1364) for failure to follow the investigational plan. These issues are unlikely to significantly impact the quality or the

integrity of the data submitted in support of this NDA. Data from the five foreign clinical investigator sites are acceptable for use in support of the indication for this application.

Note: The final EIRs for the above inspections were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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/s/

SHARON K GERSHON
12/15/2014

SUSAN D THOMPSON
12/15/2014

KASSA AYALEW
12/15/2014

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 25, 2014
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 206143
Product Name and Strength:	Corlanor (ivabradine) Tablets, 5 mg and 7.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen Inc.
Submission Date:	June 27, 2014
OSE RCM #:	2014-1252
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As a part of the New Drug Application, this review evaluates the proposed container labels, carton labeling, and Prescribing Information for Corlanor (ivabradine) Tablets for areas of vulnerability that could lead to medication errors.

The Applicant indicated they intend to launch only the bottle configurations upon initial marketing approval as stated in correspondence dated September 29, 2014. The Applicant plans to continue to evaluate the blister pack option. Since the proposed container labels and carton labeling for the blister packaging configuration were already submitted in the June 27, 2014 submission, we evaluated both the bottle and blister pack configurations.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B- N/A
Previous DMEPA Reviews	C- N/A
Human Factors Study	D- N/A
ISMP Newsletters	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Prescribing Information and container labels to identify deficiencies that may lead to medication errors and areas for improvement. After careful review of the proposed Prescribing information, we note the absence of the ivabradine hydrochloride equivalency statement which appears on the container labels and carton labeling (e.g. 5 mg (equivalent to 5.39 mg ivabradine as hydrochloride)). After careful review of the carton labeling and container labels, we note the presentation of important product information does not follow the customary format. We also note the net quantity and the strength statements are in close proximity and are presented with equal prominence. In

addition, the principal display panel of the carton labeling and container labels appear cluttered.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

1. In Section 3: Dosage Forms and Strengths and in Section 11: Description, include the ivabradine hydrochloride equivalency statements (e.g. 5 mg (equivalent to 5.39 mg ivabradine as hydrochloride)) to be consistent with the statement provided on the carton labels and container labeling.

2. The Applicant indicated they intend to launch only the bottle configurations upon initial marketing approval as stated in correspondence dated September 29, 2014. We defer to the Review Team on whether to [redacted] (b) (4) in Section 16: How Supplied.

4.2 RECOMMENDATIONS FOR THE APPLICANT

Container Labels and Carton Labeling (Bottles and blister packs)

1. Revise the presentation of the proprietary name from all caps (i.e. TRADENAME) to title case (i.e. Corlanor) to improve readability of the name. Words set in title case are easier to read than the rectangular shape that is formed by words set in all capital letters.

2. To increase the prominence of the critically important information, relocate the strength statement to immediately below the established name, such as:

   Tradename
   (ivabradine) Tablets
   # mg

3. Remove the statement [redacted] (b) (4)" because it is redundant as the net quantity statement "# tablets" is already displayed on the lower right corner. The net quantity statement may be revised to "# film-coated tablets" if desired.

4. To clarify that each tablet contains # mg, revise the statement [redacted] (b) (4) ..." to "Each tablet contains # mg ivabradine equivalent to #.## mg ivabradine as hydrochloride."

5. Revise the statement of dosage to include the header "Usual Dose: See package insert for instructions for use and dosage information". Alternatively, if space is limited, consider simplifying the statement to "Usual Dose: See package insert for dosage information".

6. Revise the storage condition [redacted] (b) (4) to read "Store at 25°C (77° F) or controlled room temperature; excursions permitted to 15C °- 30°C (59 °- 86°F) ".

Container Label (Bottles)

1. In order to minimize clutter on the principal display panels, and to create space for the strength statement immediately below the established name, relocate the statements [redacted] (b) (4) to the side panel. The statement "Keep out of the sight and reach of children" may be relocated to the side panel or remain on the principal display panel if it does not compete with the prominence of critical information.

Carton Labeling (blister packs)

1. To create space for the strength statement immediately below the established name, relocate the statements [redacted] (b) (4) Keep out of the sight and reach of children" to the right side of the principal display panel and move down the "Rx only" statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Corlanor that Amgen, Inc. submitted on June 27, 2014.

Table 2. Relevant Product Information for Corlanor	
Active Ingredient	Ivabradine
Indication	To reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 bpm, (b) (4) maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated (b) (4)
Route of Administration	Oral
Dosage Form	Film-coated tablets
Strength	5 mg and 7.5 mg The 5 mg tablet is functionally-scored and can be divided into equal halves. (The 7.5 mg tablet is not scored)
Dose and Frequency	One tablet twice daily with food. (b) (4) . Maximum daily dose is 15 mg.
How Supplied	Bottles of 60 and 180 tablets and 60 count blister packs.
Storage	(b) (4)
Container Closure	High Density Polyethylene Bottles with (b) (4) foil induction seal and a (b) (4) closure. (b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Corlanor (ivabradine) labels and labeling submitted by Amgen Inc. on June 27, 2014.

- Prescribing Information (no image)
- Professional Sample- Carton Labeling
- Professional Sample- Blistercards
- Professional Sample- Bottle
- Carton labeling- Blister
- Container Label- Blister
- Container label- Bottle

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
11/25/2014

CHI-MING TU
11/26/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 206143

Application Type: New NDA

Name of Drug/Dosage Form: Ivabradine tablets

Applicant: Amgen Inc

Receipt Date: June 27, 2014

Goal Date: February 27, 2015

1. Regulatory History and Applicant's Main Proposals

Ivabradine, developed by Les Laboratoires Servier, is currently marketed in 64 countries for the treatment of chronic heart failure and in 100 countries for the treatment of angina. Amgen recently acquired the commercial rights for the USA and has submitted the application for the treatment of chronic heart failure.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. The Postmarketing Experience subsection should NOT include AR observed in the premarketing clinical trials. The focus should be on domestic and foreign spontaneous AR observed that were not seen in the clinical studies. Do not repeat the same AR reported under the Clinical Trials Experience subsection.
2. The regulatory statement required for Pregnancy Category (b) (4) must be included per 21 CFR 201.57(c)(9) (b) (4).

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in Filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 16, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *There is no established pharmacologic class.*

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *The date is not right justified*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXIS T CHILDERS
08/27/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206143	NDA Supplement #:NA BLA Supplement #	Efficacy Supplement Type SE- NA
Proprietary Name: CORLANOR (proposed) Established/Proper Name: Ivabradine Dosage Form: Tablet Strengths: 5 mg, 7.5 mg		
Applicant: Amgen Inc. Agent for Applicant (if applicable): NA		
Date of Application: June 27, 2014 Date of Receipt: June 27, 2014 Date clock started after UN: NA		
PDUFA Goal Date: February 27, 2015	Action Goal Date (if different): N/A	
Filing Date: August 26, 2014	Date of Filing Meeting: August 4, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: to reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling	

	☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): NA

List referenced IND Number(s): 119,939 no studies conducted under an IND though.

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Priority
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		Submitted April 30, 2014 as part of rolling review

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Not needed since electronic
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		(b) (4)
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	(b) (4)
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-NDA 1/23/14 Top line 1/22/14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 4, 2014

NDA #: 206143

PROPRIETARY NAME: Corlanor (proposed)

ESTABLISHED/PROPER NAME: Ivabradine

DOSAGE FORM/STRENGTH: 5 and 7.5 mg

APPLICANT: Amgen

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): to reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm). (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4)

BACKGROUND: Ivabradine, developed by Les Laboratoires Servier, slows heart rate by modulating pacemaker activity in the sinus node. It is currently marketed in 64 countries for the treatment of chronic heart failure and in 100 countries for the treatment of angina. Amgen recently acquired the commercial rights for the USA.
There is not an active IND. Prior to submission there was a Pre-NDA and Top-Line Results meeting with Amgen to discuss the submission
The clinical development of Ivabradine consisted of 5 Phase 2 studies in chronic heart failure, a single large, randomized, placebo-controlled outcomes study entitled Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial (SHIFT) The SHIFT data will provide the primary support for the safety and efficacy of ivabradine for this indication. BEAUTIFUL, a phase 3 international, multicenter, randomized, double-blind, parallel group, placebo-controlled, long –term outcomes study assessing the effects of ivabradine on mortality and cardiovascular events in patients with stable CAD and left ventricular systolic dysfunction will provide supportive information. In addition, several studies have been conducted in patients with stable angina pectoris.
The proposed doses are 5 and 7.5 mg for the treatment of heart failure.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alexis Childers	Y

	CPMS/TL:	Ed Fromm	N
Cross-Discipline Team Leader (CDTL)	Tom Marciniak		Y
Clinical	Reviewer:	Preston Dunnmon Nhi Beasley	Y Y
	TL:	Tom Marciniak	Y

Clinical Pharmacology	Reviewer:	Martina Sahre	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jean Wu	Y
	TL:	Al DeFelice	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Mohammad Rahman	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Wendy Wilson Pei-I Chu	Y Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Janine Stewart	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	Danny Gonzalez	Y
	TL:	Kim Lehrfeld	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	N
	TL:	Susan Thompson	N
Biopharmaceutics	Sandra Suarez		Y
Pharmacometrics	Sreedharan Sabarinath		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**: will have comments for the filing letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☒ YES Date if known: January 2015 ☐ NO ☐ To be determined

If no, for an NME NDA or original BLA , include the reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: will have comments for filing letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: will have comments for the filing letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: will have requests for filing letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☒ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☒ NO
• What late submission components, if any, arrived after 30 days?	It was agreed at the pre-NDA meeting that the sponsor could submit section II of the OSI request within 5 days of the Agency selecting clinical sites for inspection. The sites were sent to the sponsor on 8/11/14
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger, MD	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): September 25, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): TBD

Comments:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): will be send with the day 60 filing letter Review Classification: ☐ Standard Review ☒ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74. Sent in Day 60 letter
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXIS T CHILDERS
08/18/2014

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 8/6/2014

To: Ni Khin, Division Director, DGCPC
Kassa Ayalew, M.D., Branch Chief, GCPAB
Susan Leibenhaut, M.D., Acting Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Sharon Gershon, Pharm.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Preston Dunnmon/ DCRP*
Norman Stockbridge /DCRP

From: *Alexis Childers/ DCRP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: 206143
IND#: none
Applicant: Amgen
Phone: (301) 944-5400
Email: ckubik@amgen.com
Regulatory Point of Contact: Christine Kubik, Senior Manager, Regulatory Affairs
Regulatory Point of Contact Phone: (301) 944-5364
Regulatory Point of Contact Email: ckubik@amgen.com

Drug Proprietary Name: Corlanor (proposed)
Generic Drug Name: Ivabradine
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): to reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4).

DGCPC/OSI Consult
version: 09/28/2011

PDUFA:
Action Goal Date: February 27, 2015
Inspection Summary Goal Date: December 15, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Donova, Temenuga 1 St Georgi Sofiiski Str Sofia, 1431 BGR Eastern Europe phone:00 359 2 92 30 720 fax: email:	4250	CL3-16257-063	35	For the treatment of chronic heart failure (b) (4) with left ventricular (b) (4) in patients in sinus rhythm and with heart rate ≥ 70 bpm, (b) (4) including beta-blocker therapy or when beta-blocker therapy is contraindicated (b) (4)
Gersamija, Arcil Viestura street 5, Dauga Vpils LV 5403 LVA Eastern Europe phone:00371 54 23 572 00371 291 26 114 fax: email:arcil-gersamija@inbox.lv	4313	CL3-16257-063	71	For the treatment of chronic heart failure (b) (4) with left ventricular (b) (4) in patients in sinus rhythm and with heart rate > 70 bpm, (b) (4) including beta-blocker therapy or when beta-blocker therapy is contraindicated (b) (4)
Macarie, Cezar Sos. Fundeni 258, Sect 2 , Bucharest 22328 ROU Eastern Europe phone:4021 317 52 33 fax: email:cmacarie_cemacarie@yahoo.com	1352	CL3-16257-063	92	For the treatment of chronic heart failure (b) (4) with left ventricular (b) (4) in patients in sinus rhythm and with heart rate > 70 bpm, (b) (4) including beta-blocker therapy or when beta-blocker therapy is contraindicated (b) (4)
Marchev, Sotir 67A, Stoletov Blvd. Sofia, 1233 BGR Eastern Europe phone:00359888619959 00359 29268 237 fax: email:	4232	CL3-16257-063	53	For the treatment of chronic heart failure (b) (4) with left ventricular (b) (4) in patients in sinus rhythm and with heart rate > 70 bpm, (b) (4) including beta-blocker therapy or when beta-blocker therapy is contraindicated (b) (4)

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Opris, Maria Gh. Marinescu str. 50 , Tg. Mures 540136 ROU Eastern Europe phone:40744 626 571 0040265212111 fax:40265 210 605 email:m-opris2000@yahoo.com	1364	CL3-16257-063	45	For the treatment of chronic heart failure (b) (4) with left ventricular (b) (4) in patients in sinus rhythm and with heart rate > 70 bpm, (b) (4) including beta-blocker therapy or when beta-blocker therapy is contraindicated (b) (4)

III. Site Selection/Rationale

Site Information

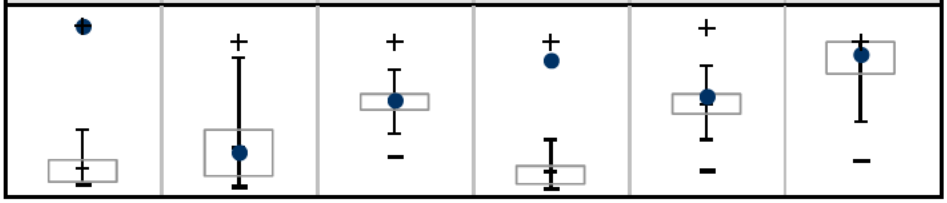
STUDY:	CL3-16257-063	**SITEID:**	1352

NAME	Macarie, Cezar
LOCATION	Sos. Fundeni 258, Sect 2 , Bucharest, ROU 22328
PHONE/FAX	4021 317 52 33 /
EMAIL	cmacarie_cemacarie@yahoo.com

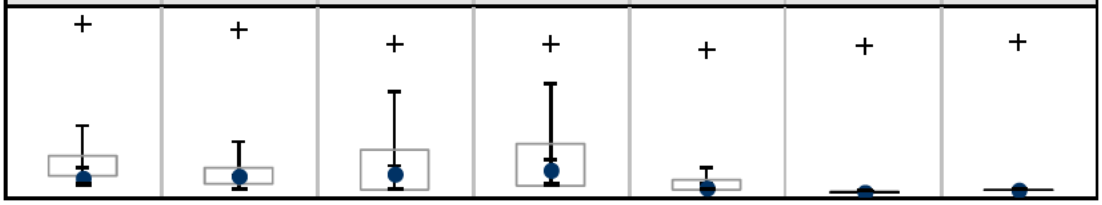
RANK	1	**FINLDISC**	143223.9	**COMPLAINT**	0
SITE RISK	15.0	**OAI**	0	**TSLI**	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	92	1.00	1.00	25.00	6.68	100%
Study Rate	10	0.26	-0.04	2.75	-0.16	91%
Min	1	0.00	-1.00	0.00	-6.35	17%
Site	92	0.24	0.01	22.00	0.47	92%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	19.0	11.0	100%	100%	2.0	5.0	21
Study Rate	2.1	1.0	16%	18%	0.1	0.0	0
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.8	0.9	11%	11%	0.0	0.0	0



Site Memo

Site 1352 Cezar Macarie – highest enrollment (92), high no. deaths (3 active, 7 placebo) high financial disclosure, average number of SAEs reported, Bucharest, Romania

Site Information

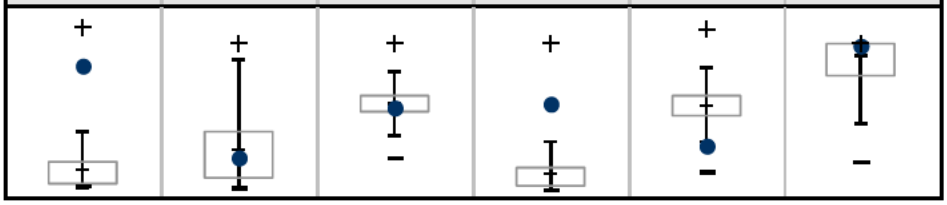
STUDY:	CL3-16257-063	SITEID:	4313

NAME	Gersamija, Arcil
LOCATION	Viestura street 5 , Dauga Vpils, LVA LV 5403
PHONE/FAX	00371 54 23 572 00371 291 26 114 /
EMAIL	arcil-gersam ja@inbox.lv

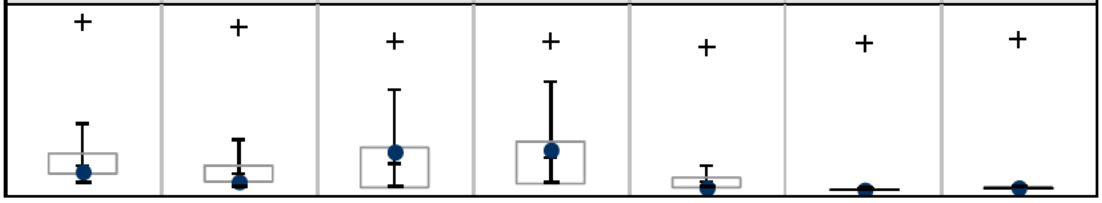
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	13.2	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	92	1.00	1.00	25.00	6.68	100%
Study Rate	10	0.26	-0.04	2.75	-0.16	91%
Min	1	0.00	-1.00	0.00	-6.35	17%
Site	71	0.21	-0.10	15.00	-3.79	99%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	19.0	11.0	100%	100%	2.0	5.0	21
Study Rate	2.1	1.0	16%	18%	0.1	0.0	0
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.4	0.3	24%	24%	0.0	0.0	0



Site Memo

Site 4313, Arcil Gersamija – Latvia, high enrollment (71), high number of deaths (7 active, 10 placebo); below average SAEs reported, Hazard ration 0.57

Site Information

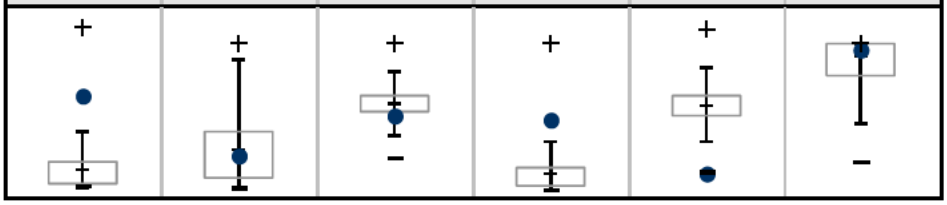
STUDY:	CL3-16257-063	SITEID:	4232

NAME	Marchev, Sotir
LOCATION	67A, Stoletov Blvd. Sofia, , BGR 1233
PHONE/FAX	00359888619959 00359 29268 237 /
EMAIL	0

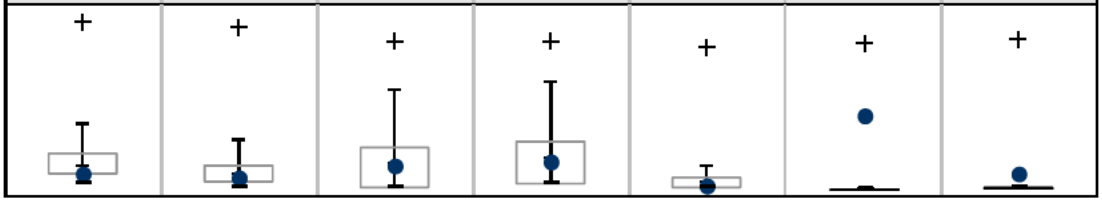
RANK	5	FINLDISC	0	COMPLAINT	0
SITE RISK	10.7	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	92	1.00	1.00	25.00	6.68	100%
Study Rate	10	0.26	-0.04	2.75	-0.16	91%
Min	1	0.00	-1.00	0.00	-6.35	17%
Site	53	0.23	-0.24	12.00	-6.35	96%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	19.0	11.0	100%	100%	2.0	5.0	21
Study Rate	2.1	1.0	16%	18%	0.1	0.0	0
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.1	0.6	15%	15%	0.0	2.5	2



Site Memo

Site 4232 Sotir Marchev (Bulgaria); Hazard ratio .29 enrolled 53, never been inspected, below average SAEs reported.

Site Information

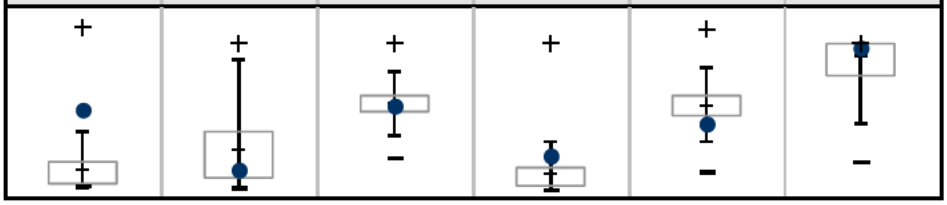
STUDY:	CL3-16257-063	SITEID:	1364

NAME	Opris, Maria
LOCATION	Gh. Marinescu str. 50 , Tg. Mures, ROU 540136
PHONE/FAX	40744 626 571 0040265212111 / 40265 210 605
EMAIL	m-opris2000@yahoo.com

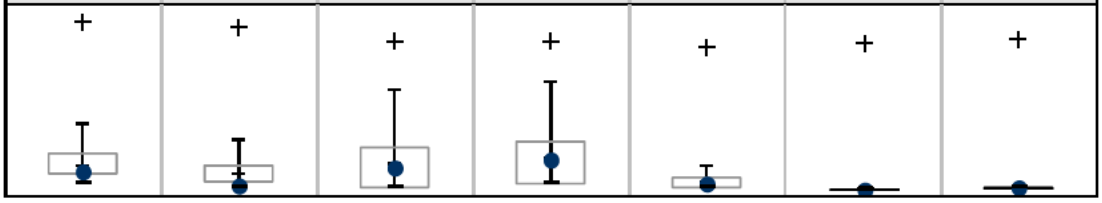
RANK	18	FINLDISC	0	COMPLAINT	0
SITE RISK	7.9	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	92	1.00	1.00	25.00	6.68	100%
Study Rate	10	0.26	-0.04	2.75	-0.16	91%
Min	1	0.00	-1.00	0.00	-6.35	17%
Site	45	0.13	-0.08	6.00	-1.83	98%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	19.0	11.0	100%	100%	2.0	5.0	21
Study Rate	2.1	1.0	16%	18%	0.1	0.0	0
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.3	0.0	13%	16%	0.0	0.0	0



Site Memo

Site 1364 Maria Opris (Romania); hazard ratio .48, enrolled 45 subjects, never been inspected. High enrollment with very low SAEs reported

Site Information

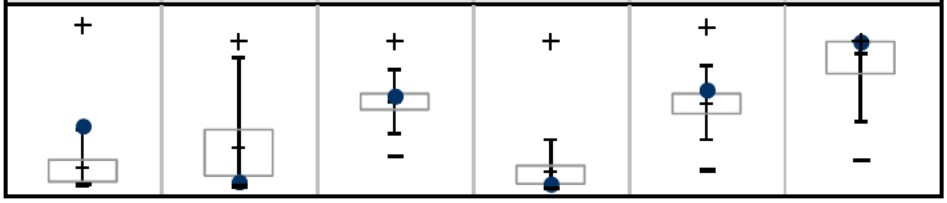
STUDY:	CL3-16257-063	SITEID:	4250

NAME	Donova, Temenuga
LOCATION	1 St Georgi Sofiiski Str Sofia, , BGR 1431
PHONE/FAX	00 359 2 92 30 720 /
EMAIL	0

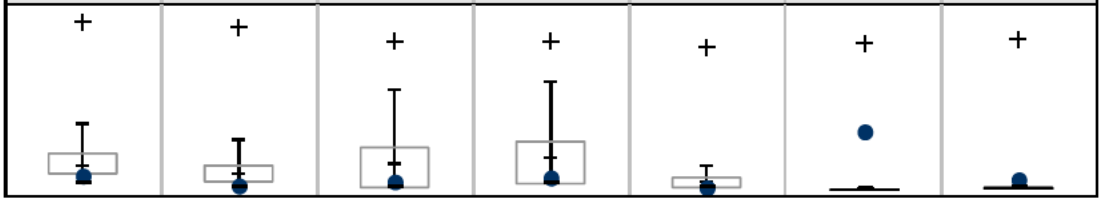
RANK	27	FINLDISC	0	COMPLAINT	0
SITE RISK	6.5	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	92	1.00	1.00	25.00	6.68	100%
Study Rate	10	0.26	-0.04	2.75	-0.16	91%
Min	1	0.00	-1.00	0.00	-6.35	17%
Site	35	0.03	0.06	1.00	1.00	100%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	19.0	11.0	100%	100%	2.0	5.0	21
Study Rate	2.1	1.0	16%	18%	0.1	0.0	0
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.9	0.1	3%	3%	0.0	2.0	1



Site Memo

Site 4250 Temenuga Donova (Bulgaria). high enrollment (35), low reporting rate for efficacy events (only one on treatment) and SAEs

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

  *See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

Rationale for the inspection of each selected site is given above as a "site memo".

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

___ There are insufficient domestic data
_x_ Only foreign data are submitted to support an application
___ Domestic and foreign data show conflicting results pertinent to decision-making
___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
___ Other (specify)

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection because of the following reasons: High enrollment, and/or exceptionally high efficacy result in favor of the experimental drug, and/or exceptionally low adverse event reporting, and/or lack of prior FDA inspection and/or high financial disclosure. This study was not conducted under a US IND, was not submitted in advance for FDA assessment and comment, and was completed over four years ago. All sites were OUS sites.

Sites are prioritized in the following order for inspection:

1. Site 1352
2. Site 4313
3. Site 4232
4. Site 1364
5. Site 4250

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Alexis Childers* at 301-796-

Concurrence: (as needed)

Tom Marciniak_____ Medical Team Leader
Preston Dunmmon_08/06/2014_, Nhi Beasley 8/6/2014_____ Medical Reviewers

Norman Stockbridge_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for OSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXIS T CHILDERS
08/08/2014

NORMAN L STOCKBRIDGE
08/09/2014

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 9, 2013

From: CDER DCRP QT Interdisciplinary Review Team

To: Alexis Childers, RPM
DCRP

Subject: QT-IRT Consult to NDA 206143

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated regarding Pre-NDA meeting (TQT waiver request). The QT-IRT received and reviewed the following materials:

- Your consult
- Summary of Nonclinical and Clinical QT/QTc analyses for Ivabradine

QT-IRT Comments for DCRP

Question 8: Does the Agency agree that the effect of ivabradine on the QT interval has been adequately characterized in the information previously submitted as a presubmission to NDA 206143 (proposed submission date October 3, 2013, #0004), and that a thorough QT (TQT) study is not required?

QT-IRT response: A TQT study is not required because we do not consider that it will adequately assess ivabradine's proarrhythmic liability due to the confounding effects of the large decrease in heart rate. Torsade de pointes cases reported in patients treated with ivabradine should be stated in the label under warning and precautions.

BACKGROUND

Ivabradine is developed for the treatment of several cardiovascular diseases. Sponsor is requesting a Type B pre-NDA meeting to review the data currently available to support a marketing application for ivabradine in chronic heart failure.
Ivabradine reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f-current (I_f), resulting in heart rate reduction without affecting blood pressure, myocardial contractility, myocardial relaxation, or coronary vascular tone.

Nonclinical Evaluation

Ivabradine and its major metabolite, S18982, were evaluated for the potential to prolong QT interval in vitro and in vivo in dedicated cardiovascular safety pharmacology studies. This nonclinical data demonstrates hERG inhibition and APD prolongation, but only at high concentrations relative to clinical exposure, with no evidence of QTc prolongation in vivo in telemeterized animals given doses that produce high plasma concentrations relative to clinical exposure.
Thus, the nonclinical profile supports a low risk for QT prolongation clinically. That said, a drug that lowers heart rate independent of adrenergic or calcium channel blockade could increase risk for bradycardia-dependent arrhythmias, including torsade de pointes.

Clinical Experience

From QTc Document

Table 1 presents the mean changes in QT, QTcB, QTcF, and QTcP intervals from baseline to last and highest values on treatment by treatment group in the Safety ECG Set . For ivabradine, uncorrected QT increased by 24.6 msec (consistent with the heart rate reduction observed), while the mean QTcB interval slightly decreased from baseline to the last value under treatment (8 msec) and the mean QTcF interval increased from baseline to the last value under treatment (3 msec) in the ivabradine and atenolol groups (groups in which uncorrected QT is expected to be prolonged due to heart rate reduction). The mean QTcP showed stability in all treatment groups.

Regarding the highest value under treatment, an increase in the QTcP interval was seen in all treatment groups (9.3 ± 19.7 msec in the ivabradine group, 3.5 ± 16.5 msec in the placebo group, 16.0 ± 16.3 msec in the atenolol group, and 3.9 ± 19.4 msec in the amlodipine group), as also shown for QTcB (2.0 ± 22.8 msec in the ivabradine group, 3.4 ± 20.1 msec in the placebo group, 8.8 ± 20.8 msec in the atenolol group, and 5.1 ± 21.8 msec in the amlodipine group), and for QTcF (11.5 ± 19.5 msec in the ivabradine group, 3.7 ± 16.0 msec in the placebo group, 18.3 ± 16.0 msec in the atenolol group and 3.7 ± 19.2 msec in the amlodipine group).

Table 1. Mean Changes in QT, QTcB, QTcF, and QTcP Intervals (msec) in Lead D2 from Baseline to the Last Value and Highest Value on Treatment by Treatment Group – Pool of Studies CL3-16257-019, CL3-16257-021, CL3-16257-023 and CL3-16257-057

Uncorrected QT Baseline End		Ivabradine N = 1250	Placebo N = 329	Atenolol N = 83	Amlodipine N = 228
Baseline	Mean ± SD	382.3 ± 29.4	390.5 ± 22.1	381.2 ± 25.9	375.5 ± 30.5
End	Mean ± SD	406.8 ± 33.0	393.5 ± 26.2	407.5 ± 31.7	373.6 ± 31.2
Highest	Mean ± SD	418.1 ± 32.7	400.0 ± 25.3	426.3 ± 27.9	379.5 ± 31.6
End - Baseline	Mean ± SD	24.6 ± 28.0	3.0 ± 22.7	26.3 ± 29.0	-1.9 ± 25.8
	E (SE)[a]	24.6 (0.8)	3.0 (1.3)	26.3 (3.2)	-1.9 (1.7)
	95% CI	[23.0; 26.1]	[0.5; 5.4]	[20.0; 32.7]	[-5.3; 1.4]
Highest - Baseline	Mean ± SD	35.9 ± 27.3	9.4 ± 21.2	45.1 ± 26.6	4.1 ± 24.6
	E (SE)[a]	35.9 (0.8)	9.4 (1.2)	45.1 (2.9)	4.1 (1.6)
	95% CI[b]	[34.4;37.4]	[7.1;11.7]	[39.3;50.9]	[0.8;7.3]
Corrected QT		N = 1243	N = 329	N = 81	N = 228
QTc Bazett					
Baseline	Mean ± SD	410.8 ± 26.1	412.2 ± 21.5	406.9 ± 26.5	404.4 ± 25.0
End	Mean ± SD	403.0 ± 26.6	409.9 ± 23.2	400.8 ± 27.0	403.0 ± 25.7
Highest	Mean ± SD	412.8 ± 26.9	415.6 ± 22.2	415.6 ± 27.9	409.6 ± 25.6
End - Baseline	Mean ± SD	-7.9 ± 23.2	-2.3 ± 20.4	-6.1 ± 23.5	-1.4 ± 22.4
	E (SE)[a]	-7.9 (0.7)	-2.3 (1.1)	-6.1 (2.6)	-1.4 (1.5)
	95% CI[b]	[-9.2;-6.6]	[-4.5;-0.1]	[-11.2;-0.9]	[-4.3;1.5]
Highest - Baseline	Mean ± SD	2.0 ± 22.8	3.4 ± 20.1	8.8 ± 20.8	5.1 ± 21.8
	E (SE)[a]	2.0 (0.6)	3.4 (1.1)	8.8 (2.3)	5.1 (1.4)
	95% CI[b]	[0.7;3.2]	[1.2;5.6]	[4.2;13.3]	[2.3;8.0]
QTc Fridericia					
Baseline	Mean ± SD	400.8 ± 23.5	404.7 ± 19.7	397.7 ± 21.9	394.2 ± 22.5
End	Mean ± SD	404.0 ± 24.6	404.1 ± 18.9	402.5 ± 23.0	392.7 ± 23.4
Highest	Mean ± SD	412.3 ± 24.7	408.4 ± 18.5	416.0 ± 24.5	397.9 ± 23.7
End - Baseline	Mean ± SD	3.1 ± 19.8	-0.6 ± 16.0	4.8 ± 17.5	-1.6 ± 19.9
	E (SE)[a]	3.1 (0.6)	-0.6 (0.9)	4.8 (1.9)	-1.6 (1.3)
	95% CI[b]	[2.0;4.2]	[-2.4;1.1]	[1.0;8.7]	[-4.1;1.0]
Highest - Baseline	Mean ± SD	11.5 ± 19.5	3.7 ± 16.0	18.3 ± 16.0	3.7 ± 19.2
	E (SE)[a]	11.5 (0.6)	3.7 (0.9)	18.3 (1.8)	3.7 (1.3)
	95% CI[b]	[10.4;12.5]	[2.0;5.4]	[14.8;21.8]	[1.2;6.2]
QTc Population					
Baseline	Mean ± SD	402.9 ± 23.7	406.3 ± 19.9	399.6 ± 22.6	396.3 ± 22.6
End	Mean ± SD	403.7 ± 24.7	405.3 ± 19.4	402.0 ± 23.4	394.9 ± 23.4
Highest	Mean ± SD	412.2 ± 24.8	409.8 ± 18.8	415.6 ± 24.9	400.3 ± 23.8
End - Baseline	Mean ± SD	0.8 ± 20.0	-1.0 ± 16.5	2.4 ± 18.2	-1.4 ± 20.0
	E (SE)[a]	0.8 (0.6)	-1.0 (0.9)	2.4 (2.0)	-1.4 (1.3)
	95% CI[b]	[-0.3;2.0]	[-2.8;0.7]	[-1.7;6.4]	[-4.0;1.2]
Highest - Baseline	Mean ± SD	9.3 ± 19.7	3.5 ± 16.5	16.0 ± 16.3	3.9 ± 19.4
	E (SE)[a]	9.3 (0.6)	3.5 (0.9)	16.0 (1.8)	3.9 (1.3)
	95% CI[b]	[8.2;10.4]	[1.7;5.2]	[12.4;19.6]	[1.4;6.5]

End: Last value under treatment; Highest: Highest value on treatment
N = Number of patients in the treatment group.
n = Number of patients with an available baseline and at least one available post-baseline value on treatment in each treatment group
[a] E (SE): Estimate (Standard Error) of the difference End - Baseline (parametric approach without adjustment)
[b] 95% CI: 95% CI of the estimate (two-sided) based on the overall general linear model (least squares norm)
CI = confidence interval; E = estimate; SD = standard deviation; SE = standard error.

Mean QT/QTc Values in Study CL2-16257-047.

The primary objective of CL2-16257-047 was to describe the cardiac and overall safety of ivabradine on an oral dose escalating regimen over a 3-week treatment period in patients with proven CAD. Each dose of ivabradine was administered for one week (10 mg BID on days 0-7, 15 mg BID on days 8 to14, and 20 mg BID on days 15 to 21) following verification of the up-titration criterion (QTcB at the peak of drug activity < 480 msec) in each patient. Atenolol, the active comparator, was given at a fixed dose of 50 mg once daily (QD) for the 3 weeks of the study.

In the ivabradine group, at the trough of drug activity, heart rate was decreased by 11.5 ± 7.9 bpm at day (D) 7, by 15.4 ± 8.5 bpm at D 14 and by 16.7 ± 7.3 bpm at D21. At the peak of drug activity, heart rate reduction was 15.8 ± 8.6 bpm, 19.5 ± 8.7 bpm and 22.1 ± 8.7 bpm at D7, D14 and D21 respectively.

Table 2 presents the mean changes in uncorrected QT, QTcB, QTcF, and QTcP intervals from baseline to last and highest values on treatment by treatment group in study CL2-16257-047 on ECGs performed at the peak of drug activity. Uncorrected QT increased more in the ivabradine group as compared to atenolol, consistent with the more marked decrease in heart rate for ivabradine as compared to atenolol. The QTcB value decreased from baseline to the last value under treatment in both treatment groups. QTcF increased by 6.7 msec in the ivabradine group with no change in the atenolol group while QTcP increased by 0.8 msec in the ivabradine group.

Table 2. Mean Changes in QTcB, QTcF, and QTcP Intervals (msec) in Lead D2, from Baseline to the Last Value and Highest Value on Treatment – ECGs at Peak of Drug Activity – Study CL2-16257-047

		Ivabradine N = 51 n = 43	Atenolol N = 27 n = 22
Uncorrected QT			
Baseline	Mean ± SD	386.5 ± 29.2	386.8 ± 30.6
End	Mean ± SD	449.6 ± 34.9	425.9 ± 31.2
Highest	Mean ± SD	452.2 ± 33.6	430.1 ± 30.0
End - Baseline	Mean ± SD	63.1 ± 28.2	39.1 ± 22.6
	E (SE)[a]	63.1 (4.3)	39.0 (4.8)
	95% CI[b]	[54.4;71.8]	[29.0;49.1]
Highest - Baseline	Mean ± SD	65.7 ± 26.0	43.3 ± 21.8
	E (SE)[a]	65.7 (4.0)	43.3 (4.7)
	95% CI[b]	[57.7;73.7]	[33.6;53.0]
QTc Bazett			
Baseline	Mean ± SD	409.8 ± 24.7	423.9 ± 26.8
End	Mean ± SD	389.6 ± 26.6	401.8 ± 26.6
Highest	Mean ± SD	401.2 ± 26.9	408.2 ± 28.3
End - Baseline	Mean ± SD	-20.2 ± 18.6	-22.1 ± 12.6
	E (SE)[a]	-20.2 (2.8)	-22.0 (2.7)
	95% CI[b]	[-25.9;-14.5]	[-27.6;-16.5]
Highest - Baseline	Mean ± SD	-8.6 ± 15.7	-15.7 ± 10.9
	E (SE)[a]	-8.6 (2.4)	-15.7 (2.3)
	95% CI[b]	[-13.4;-3.7]	[-20.5;-10.8]
QTc Fridericia			
Baseline	Mean ± SD	401.6 ± 21.9	410.7 ± 21.9
End	Mean ± SD	408.3 ± 25.6	409.6 ± 24.8
Highest	Mean ± SD	414.3 ± 25.4	413.9 ± 26.4
End - Baseline	Mean ± SD	6.7 ± 15.6	-1.2 ± 12.0
	E (SE)[a]	6.7 (2.4)	-1.2 (2.6)
	95% CI[b]	[1.9;11.5]	[-6.5;4.1]
Highest - Baseline	Mean ± SD	12.7 ± 13.9	3.2 ± 12.7
	E (SE)[a]	12.7 (2.1)	3.2 (2.7)
	95% CI[b]	[8.5;17.0]	[-2.5;8.8]
QTc Population			
Baseline	Mean ± SD	403.2 ± 22.1	413.3 ± 22.6
End	Mean ± SD	404.0 ± 25.5	407.7 ± 25.1
Highest	Mean ± SD	411.1 ± 25.5	412.5 ± 26.7
End - Baseline	Mean ± SD	0.81 ± 15.7	-5.6 ± 11.5
	E (SE)[a]	0.8 (2.4)	-5.6 (2.4)
	95% CI[b]	[-4.0;5.6]	[-10.7;-0.5]
Highest - Baseline	Mean ± SD	7.9 ± 13.8	-0.7 ± 11.6
	E (SE)[a]	7.9 (2.1)	-0.7 (2.5)
	95% CI[b]	[3.6;12.1]	[-5.9;4.4]

End: Last value under treatment; Highest: Highest value on treatment
N = Number of patients in the treatment group
n = Number of patients with an available baseline and at least one available post-baseline value on treatment in each treatment group
[a] E (SE): Estimate (Standard Error) of the difference End - Baseline (parametric approach without adjustment)
[b] 95% CI: 95% confidence interval of the estimate (two-sided) based on the overall general linear model (least squares norm)
SD = standard deviation

Incidence of Treatment Emergent Adverse Events of Interest Versus Placebo in the Pooled Phase 2 and 3 Studies

Two emergent cases of torsade de pointes were observed in the ivabradine group. The 2 cases occurred in study CL3-063 (SHIFT), a clinical trial that enrolled patients with symptomatic systolic heart failure, and both cases were confounded by multiple clinical risk factors that predispose patients to torsade de pointes.

One (Subject 000260) case occurred in the context of severe hypokalemia in a patient taking loop diuretics, with a serum potassium of 2.7 mEq/L upon presentation with ventricular tachycardia. The other case (Subject 005041) occurred in a patient taking loop diuretics with a history of myocardial infarctions and ischemic cardiomyopathy. Subject 005041's initial arrhythmia was atrial flutter with 1:1 conduction, followed by sustained monomorphic ventricular tachycardia that was treated with the anti-arrhythmic drug lidocaine, and then degenerated into torsade de pointes. Heart failure, structural heart disease, history of myocardial infarction, hypokalemia and treatment with diuretics are known major risk factors for torsade de pointes (Drew et al, 2010).

Table 18. Treatment Emergent Adverse Events of Interest in the Pool of Phase 2/3 Studies (N = 22514): Ivabradine Versus Placebo

	Ivabradine N = 12232, NPY = 13953			Placebo N = 9443, NPY = 13849			E (SE)[d]	95% CI[e]	p value[f]
Preferred Term	n[a]	%[b]	%PY[c]	n[a]	%[b]	%PY[c]			
All	681	5.57	4.88	675	7.15	4.87	0.01 (0.26)	[-0.50, 0.51]	1.000
Sudden death	326	2.67	2.34	304	3.22	2.20	0.14 (0.18)	[-0.21, 0.49]	0.444
Sudden cardiac death	73	0.60	0.52	68	0.72	0.49	0.03 (0.09)	[-0.14, 0.20]	0.736
Ventricular fibrillation	42	0.34	0.30	25	0.26	0.18	0.12 (0.06)	[0.00, 0.24]	0.050
Ventricular tachycardia	134	1.10	0.96	144	1.52	1.04	-0.08 (0.12)	[-0.32, 0.16]	0.508
Ventricular flutter	1	0.01	0.01	0	0	0	0.01 (0.01)	[-0.02, 0.04]	1.000
Torsade de pointes	2	0.02	0.01	0	0	0	0.01 (0.01)	[-0.02, 0.05]	0.500
Ventricular tachyarrhythmia	0	0	0	1	0.01	0.01	-0.01 (0.01)	[-0.04, 0.02]	0.498
Ventricular arrhythmia	18	0.15	0.13	13	0.14	0.09	0.04 (0.04)	[-0.05, 0.12]	0.473
Cardiac arrest	4	0.03	0.03	3	0.03	0.02	0.01 (0.02)	[-0.04, 0.05]	1.000
Loss of consciousness	11	0.09	0.08	11	0.12	0.08	0.00 (0.03)	[-0.07, 0.07]	1.000
Syncope	73	0.60	0.52	103	1.09	0.74	-0.22 (0.10)	[-0.41, -0.03]	0.023
Presyncope	21	0.17	0.15	23	0.24	0.17	-0.02 (0.05)	[-0.11, 0.08]	0.765
Epilepsy	3	0.02	0.02	2	0.02	0.01	0.01 (0.02)	[-0.03, 0.05]	1.000
Grand mal convulsion	1	0.01	0.01	0	0	0	0.01 (0.01)	[-0.02, 0.04]	1.000
Tonic convulsion	1	0.01	0.01	0	0	0	0.01 (0.01)	[-0.02, 0.04]	1.000
Convulsions local	1	0.01	0.01	0	0	0	0.01 (0.01)	[-0.02, 0.04]	1.000

[a] Number of patients with at least one emergent adverse event for a given Preferred Term
[b] Percentage of total number of patients in the treatment group
[c] Number of patients with at least one emergent adverse event for a given Preferred Term per 100 patient-years
[d] Estimate (Standard Error) of the difference between groups (ivabradine minus placebo) for %PY
[e] 95% confidence interval of the estimate
[f] Two-sided Fisher's exact test
PY: Patient years

If considering only study CL3-16257-063 (SHIFT), 36 cases were reported by the investigators as VF, with a higher incidence in the ivabradine group as compared to placebo (Table 19). However, an inverse trend was present for ventricular tachycardia.

Table 19. Study CL3-16257-063 - Ventricular Fibrillation - on Treatment - Crude Rates and per 100 Patient-Years - as Assigned by Investigators, in the Safety Set (N = 6492)

	Ivabradine (N = 3232)			Placebo (N = 3260)		
	n	%	%PY	n	%	%PY
Ventricular fibrillation	24	0.7	0.4	12	0.4	0.2
Ventricular tachycardia	60	1.9	1.1	70	2.2	1.3

N: number of patients in the considered treatment group
n: number of patients having experienced the endpoint
%PY: annual incidence rate

Evaluation of QT in Paced Patients

A specific study was conducted to evaluate a potential heart-rate-independent, direct effect of ivabradine on the QT interval. Sequential fixed pacing rates were applied to patients treated with ivabradine in order to suppress the heart rate lowering effect of ivabradine. Patients with a dual chamber pacemaker underwent a non-invasive electrophysiologic procedure with consecutive fixed pacing rates before and after ivabradine or placebo administration for 3.5 days (Appendix 5). Patients were randomized either to ivabradine 5 mg BID (n = 8) or to ivabradine 10 mg BID (n = 8) or to placebo (n = 9).

At fixed pacing rates of 80 to 110 bpm, ivabradine treatment (5 and 10 mg BID) did not lead to prolongation of the QT interval (Table 10)**.** All observed changes were comparable to those on placebo. No direct pharmacological effect of ivabradine at either dosewas observed on QT interval when measured at different sequential fixed pacing rates. The mean change of 8.33 msec for the paced rate of 110 bpm (Figure 4**)** is due to one subject whose T wave fused with the atrial pacing spike, with the T wave offset fusing with the P wave onset leading to an inaccurate measurement of the QT interval. In this subject, the apparent change in QT was 25 msec, whereas the changes in the other 2 subjects in this dose group were +2 and -2 msec.

Table 10. QT Interval Data for Ivabradine with Fixed Pacing Rates

		Mean values ± SD (msec) at baseline (D0) and at D4								Mean changes ± SD (msec) at D4 *versus* baseline (D0)			
		Pacing rates (AAI[a]) (bpm)								Pacing rates (AAI[a]) (bpm)			
Treatment group	All patients	80		90		100		110		80	90	100	110
Uncorrected QT interval		D0	D4	D0	D4	D0	D4	D0	D4				
Iva 5 mg BID n_a = 8	Patients (n)	7	7	6	6	5	5	6	6	7	6	5	6
	Mean	377.7	375.3	364.7	362.8	349.6	350.8	335.7	336.0	-2.43	-1.83	1.20	0.33
	SD	23.9	23.4	26.0	25.8	26.8	22.4	23.2	18.4	5.47	3.76	6.69	7.58
Iva 10 mg BID n_a = 8	Patients (n)	7	7	7	6	7	7	3	3	7	6	7	3
	Mean	369.9	369.1	350.9	350.3	336.6	336.6	311.3	319.7	-0.71	-2.67	0.00	8.33
	SD	29.2	22.0	20.4	23.6	23.2	25.0	-	-	8.62	3.39	6.16	-
Placebo n_a = 9	Patients (n)	5	6	6	7	6	6	5	4	5	6	6	4
	Mean	366	363.0	341.2	339.4	342.2	326.5	315.4	320.7	0.40	-0.17	2.33	4.00
	SD	26.5	21.4	23.3	20.4	22.9	20.2	18.7	21.6	5.90	4.62	6.41	1.41

[a] AAI: Atrial pacing mode with Atrial sensing and Inhibition
bpm: beats per minute
Iva: Ivabradine
BID: Twice daily
n: number of patients
n_a: number of patients treated

Reviewer's Comments: The results of this study cannot be used to rule out small increases in QT because measurements were obtained at trough concentrations, the sample size was small, and a positive control was not used.

Postmarketing

-ECG-prolonged QT Interval

Since the introduction of ivabradine on the market, a total of 24 cases of ECG-prolonged QT interval were reported (including one case of long QT syndrome). Considering the overall estimated exposure to ivabradine since marketing authorization (ie, 1,351,798 patient-years), the overall frequency of reported cases of ECG QT prolongation is 1.77/100,000 PY. In 14 cases, concomitant heart rate lowering drugs were given with ivabradine. In 18 cases, ECG-prolonged QT interval was associated with cardiac events or other ECG abnormalities, especially bradycardia/heart rate decreased (8 cases) and severe ventricular arrhythmias (6 cases). One case of ECG-prolonged QT interval, complicated by ventricular tachycardia, and torsade de pointes in a context of hypokalemia, was reported in a 62 year-old female patient concomitantly treated with furosemide and diltiazem.

-Syncope, Pre-syncope

Syncope or pre-syncope was reported in 54 patients during the period (3.99/100,000 PY). In 22 cases, bradycardia or heart rate decrease was associated with the event; in 5 cases, complete AV block was concomitant; and in 5 cases, ventricular arrhythmia was concomitant (associated to bradycardia or heart rate decreased in 2 cases). In 47 cases, the patient recovered or was recovering, and in one case, the patient had not recovered at the time of the report. None of these events were fatal. In 6 cases, the outcome is unknown.

-Torsade de Pointes

Torsade de pointes that occurred post-marketing in patients on ivabradine occurred mostly in the context of known alternate risk factors that predispose to such events (Drew et al, 2010): concomitant loop diuretics (in 8/12 cases), patients with hypokalemia (2 cases documented) in patients receiving other drugs with heart rate lowering activities (7/12 cases) or in patients receiving concomitant contra-indicated or not recommended drug (5/12 cases), like verapamil, diltiazem, fluconazole or macrolide antibiotics). In two cases, QTc prolongation and in one case complete AV block were documented. For the other cases of severe ventricular arrhythmias, a cardiac disease known to be associated with ventricular arrhythmia (CAD, heart failure, valvulopathy) was present in all the cases.

-Sudden Death, Sudden Cardiac Death, Death and Cardiac Death

A total of 21 cases of suspected adverse drug reaction death coded with the preferred terms "sudden death", "sudden cardiac death", "death", or "cardiac death" have been reported since the marketing authorization (1.55/100,000 PY). Patients taking ivabradine are enriched for structural heart disease, ischemic heart disease and heart failure, which are major independent risk factors for ventricular arrhythmias and torsade de pointes.

Table 24. Post-marketing Adverse Drug Reactions – Clinical Relevance of Severe Ventricular Arrhythmias

CLINICAL RELEVANCE	Torsade de pointes without other ventricular arrhythmia	Torsade de pointes associated with ventricular tachycardia	VF/Vf/VT/VA
Number of cases since MA	9	3	41 ADRs in 34 cases
Temporal association (occurrence after the 1st intake of the drug)	Within 1 week: 1/9 Within 1 month: 2/9 Within 3 months: 2/9 > 3 months: 2/9 Unknown: 2/9	Within 1 week: 2/3 Unknown: 1/3	Within 1 week: 18/34 Within 1 month: 5/34 Within 3 months: 1/34 > 3 months: 1/34 Unknown: 8/34
Causality assessment	Doubtful: 9/9	Doubtful: 3/3	Doubtful: 34/34
Relevant underlying condition	Age ≥ 65y: 7/9 Female: 4/9 <u>Relevant medical history</u> • Ischemic,alcoholic or unspecified Cardiopathy: 4/9 • Valvulopathy: 1/9 • Heart failure: 6/9 <u>Relevant context</u> • Electrolytic disorders: 1/9 • Bradycardia < 50 bpm: 3/9 • QTc prolongation: 2/9 • Complete AVB: 3/9 <u>Concomitant drugs</u> • Concomitant HR lowering drugs: 6/9 • Concomitant contra-indicated or not recommended drugs: 3/9 • Concomitant loop diuretics: 6/9	Age ≥ 65y: 1/3 Female: 2/3 <u>Relevant medical history</u> • Ischemic cardiopathy: 1/3 • Alcoholism: 1/3 • Heart failure : 1/3 <u>Relevant context</u> • Electrolytic disorders: 1/3 <u>Concomitant drugs</u> • Concomitant HR lowering drugs: 1/3 • Concomitant contra-indicated or not recommended drugs: 3/3 • Concomitant loop diuretics: 2/3	Age ≥ 65y: 19/34 Female: 20/34 <u>Relevant medical history</u> • Ischemic or unsopecified cardiopathy: 5/34 • Valvulopathy: 4/34 • Heart failure: 5/34 • CAD*: 25/34 <u>Relevant context</u> • Acute ischemic event: 2/34 • Bradycardia: 4/34 • AVB: 4/34 • QT prolongation 1/34 <u>Concomitant drugs:</u> • Concomitant HR lowering drugs: 14/34 • Concomitant contra-indicated or not recommended drugs: 6/34 • Concomitant loop diuretics: 17/34
Fatal cases	1/9	1/3	8/34

MA: Marketing Authorization;
PY: patient-years;
VF: ventricular fibrillation;
Vf: ventricular flutter;
CAD: coronary artery disease;
AVB: atrioventricular block;
HR: heart rate

Reviewer's comments: Emergent cases of torsade de pointes were reported in phase 2/3 clinical trials in the ivabradine group. Cases of torsade de pointes, ventricular tachycardia and ventricular fibrillation were reported postmarketing.

Thank you for requesting our input into the development of this product under NDA 206143. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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