

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206143Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 27, 2015

Reviewer(s): Danny Gonzalez, Pharm.D., M.S.,
Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader: Kim Lehrfeld, Pharm.D., B.C.P.S.
DRISK

Acting Deputy Director: Reema Mehta, Pharm.D., M.P.H.
DRISK

Drug Name(s): Corlanor (ivabradine)

Therapeutic Class: I_f channel inhibitor

Dosage and Route: 5mg and 7.5mg film-coated tablets

Application Type/Number: NDA 206143

Submission Number: Sequence No. 0017

Applicant/sponsor: Amgen Inc.

OSE RCM #: 2014-1253

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1	INTRODUCTION	1
1.1	Product Background.....	1
1.2	Disease Background.....	2
1.3	Regulatory History.....	3
2	MATERIALS REVIEWED	3
3	REVIEW OF SAFETY CONCERNS	4
3.1	Overview of Clinical Development Program	4
4	SUMMARY OF SPONSOR'S PROPOSED LABELING FOR IVABRADINE.....	10
5	DISCUSSION.....	10
6	CONCLUSION	12
7	RECOMMENDATIONS.....	12

EXECUTIVE SUMMARY

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Corlanor (ivabradine), NDA 206143, received from Amgen Inc. (Amgen) on June 27, 2014. The Sponsor did not propose a REMS with the NDA submission.

The proposed indication is to reduce the risk of hospitalizations for worsening heart failure in patients with stable, symptomatic chronic heart failure due to a left ventricular ejection fraction < 35%, in sinus rhythm with resting heart rate \geq (b) (4) beats per minute (bpm), who are taking optimal doses of standard heart failure therapies including beta blockers, or when beta blocker therapy is contraindicated (b) (4).

Based on the currently available data, the safety concerns described in this review include atrial fibrillation, bradycardia, atrioventricular block, and teratogenicity, which were observed during the clinical development program. OSE, DRISK does not recommend that ivabradine have a REMS program for approval.

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Corlanor (ivabradine), NDA 206143. A 505(b)(1) application for Corlanor was received by the Division of Cardiovascular Products (DCRP) from Amgen Inc. (Amgen) on June 27, 2014 to treat heart failure (HF). The Sponsor did not propose a REMS for Corlanor.

1.1 PRODUCT BACKGROUND

Corlanor, ivabradine, is a novel sinus node inhibitor that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f -current (I_f), resulting in heart rate reduction with no negative effects on myocardial contractility or ventricular repolarization.

The proposed indication is to reduce the risk of hospitalizations for worsening heart failure in patients with stable, symptomatic chronic heart failure due to a left ventricular ejection fraction < 35%, in sinus rhythm with resting heart rate \geq (b) (4) beats per minute (bpm), who are taking optimal doses of standard heart failure therapies including beta blockers, or when beta blocker therapy is contraindicated (b) (4). If approved, ivabradine will be available as tablets (5 mg and 7.5 mg). The 5 mg tablets have a score line that enables them to be divided into two halves each containing 2.5 mg ivabradine.

Ivabradine, developed by Les Laboratoires Servier, is currently marketed in 64 countries for the treatment of CHF and in 100 countries for the treatment of angina. In Europe, ivabradine was first developed to treat stable angina pectoris and was granted this indication in October 2005 by the European Medicines Agency (EMA) in patients with normal sinus rhythm and intolerance or contra-indication for beta blockers. Ivabradine was later approved for an indication to treat CHF and was granted this indication by the EMA in February 2012 for CHF NYHA II to IV class with systolic dysfunction in

patients with sinus rhythm and heart rate > 75 bpm in combination with standard therapy including beta blocker therapy or when beta blocker therapy is contraindicated or not tolerated. Thus, there is a large database for ivabradine use in the post-marketing setting demonstrating an overall positive safety profile.

1.2 DISEASE BACKGROUND

Chronic heart failure is a common syndrome affecting approximately 2 to 3% of the population in many industrialized countries. Coronary artery disease (CAD) is the cause of approximately two-thirds of cases of systolic HF, although hypertension and diabetes are probable contributing factors in many cases. There are many other causes of systolic HF, which include previous viral infection, alcohol abuse, chemotherapy (e.g. doxorubicin or trastuzumab), and 'idiopathic' dilated cardiomyopathy. Even with the existing treatments, which have substantially improved outcomes in the past two decades, heart failure remains a disabling disorder that can severely affect the patient's quality of life and the prognosis is fairly poor. HF mortality rate is twice that of breast or bladder cancer and similar to that of colon cancer.

CHF due to left ventricular dysfunction, also referred to as HF with reduced Ejection Fraction (HFrEF), is substantial and growing medical problem that effects millions of adults in the United states. Class I recommendations in the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for the pharmacologic treatment of HFrEF include:¹

- Angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARB) if ACE inhibitors are not tolerated, to reduce morbidity and mortality
- Beta-blockers (bisoprolol, carvedilol, or controlled release/extended release metoprolol succinate) to reduce morbidity and mortality
- Diuretics and a low-sodium diet, if there is evidence of fluid retention to improve symptoms
- Aldosterone antagonists (provided estimated creatinine > 30 mL/min and K⁺ < 5.0 mEq/dL) to reduce morbidity and mortality.
- Hydralazine/isosorbide dinitrate (for African Americans with persistently symptomatic NYHA class III-IV heart failure) receiving optimal therapy with ACE inhibitors and beta blockers, to reduce morbidity and mortality.

In addition to the indicated pharmacotherapies for HFrEF (i.e., digoxin, ACE inhibitors, beta-blockers, etc.), Class I recommendations for the device treatment of HFrEF, including the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), are as follows:

- ICD therapy for primary prevention of sudden cardiac death (SCD) to reduce total mortality in selected patients with nonischemic dilated cardiomyopathy (DCM) or ischemic heart disease at least 40 days post-myocardial infarction (MI) with left

¹ Yancy et al, Circulation. 2013;128:e240-e327

ventricular ejection fraction (LVEF) of 35% or less and NYHA class II or III symptoms on chronic guideline-directed medical therapy (GDMT), who have reasonable expectation of meaningful survival for more than 1 year

- CRT for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT
- ICD therapy is for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.

1.3 REGULATORY HISTORY

January 23, 2014: The Agency communicated to the Sponsor at a pre-NDA meeting that based on the currently available information, the Agency does not believe a REMS program will be necessary for ivabradine. However, a final determination of the need for a REMS program will be made during the review of the application.

June 27, 2014: Amgen submitted NDA 206143 for the treatment of heart failure

October 6, 2014: The Sponsor met with the Agency for the post Mid Cycle Meeting to discuss questions related to results from the Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial (SHIFT) and Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) clinical trials. The Agency reported at this meeting that a REMS program may not be necessary to ensure that the benefits of ivabradine outweigh the risks.

2 MATERIALS REVIEWED

The following is a list of materials used to inform our review:

- Beasley N, Dunnmon P, and Marciniak T. Mid-cycle meeting minutes for ivabradine. October 21, 2014.
- Beasley N, Dunnmon P, and Marciniak T. Pre-mid-cycle meeting presentations for ivabradine. September 25, 2014.
- Dunnmon P. Clinical Review for Ivabradine. December 4, 2014.
- Wu J. Pharmacology/Toxicology NDA Review Evaluation (Reproductive and Development Toxicology) for ivabradine. November 2014.
- Amgen. Package insert for ivabradine [Draft]. September 2014.
- Amgen. EMA Risk Management Plan for ivabradine. April 2013.
- Amgen. Ivabradine. Response to Information Request. December 12, 2014. (eCTD Seq. No. 0061)
- Amgen. Ivabradine. Response to Information Request. December 19, 2014. (eCTD Seq. No. 0064)
- Amgen. Ivabradine. Response to Information Request. December 23, 2014. (eCTD Seq. No. 0065)
- Amgen. Ivabradine. Draft Medication Guide. January 16, 2015. (eCTD Seq. No. 0067).

3 REVIEW OF SAFETY CONCERNS

3.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

The pivotal clinical trial used to demonstrate efficacy in the proposed indication for heart failure was based on data from SHIFT study. The safety data was pooled from three clinical trials: SHIFT, BEAUTIFUL, and Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY). A summary of each of these studies is described below (Table 1).

Study	Study Design/Description
SHIFT	A single large, randomized, placebo-controlled outcomes study for CHF. Enrolled 6,588 patients in NYHA functional class II – IV, sinus rhythm with a heart rate of ≥ 70 bpm, an ejection fraction (EF) $\leq 35\%$, and must have had a hospitalization due to HF in the previous 12 months. Patients were randomized to ivabradine (up-titrated to a maximal dosage of 7.5 mg twice daily) or placebo, concomitantly with any of the following: a diuretic (84% of patients), digoxin (22% of patients), an ACE inhibitor (79% of patients), an ARB (14% of patients), a beta-blocker (90% of patients), or a mineralocorticoid receptor antagonist (60% of patients). Only 26% of patients were, however, on full-dose beta-blocker. The median follow-up was 23 months.
BEAUTIFUL	A randomized, double blind, placebo-controlled, multi-center, international morbidity-mortality study, with two parallel and balanced treatment arms. Enrolled 10,917 patients with stable coronary artery disease, a resting heart rate > 60 bpm, and an EF $< 39\%$. The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of incidence of the composite endpoint: cardiovascular (CV) mortality, hospital admissions for acute MI, hospital admissions for new onset or worsening heart failure (HF) in patients with CAD and LV systolic dysfunction. This study enrolled patients with coronary artery disease and a LVEF $< 39\%$
SIGNIFY	SIGNIFY was an event-driven, phase III, international, multi-center, randomized, double-blind, placebo-controlled trial with two parallel and balanced treatment arms (ivabradine and placebo) in patients with stable coronary artery disease without clinical heart failure. This trial enrolled 19,102 subjects with NYHA CHF Class I, resting heart rate ≥ 70 bpm, and EF $> 40\%$. The trial consisted of a run-in period of at least one week in which no placebo is given. The minimum study follow-up was 12 months. The primary objective was to demonstrate the

	superiority of ivabradine over placebo in the reduction of CV mortality or non-fatal MI (composite endpoint). This study enrolled patients with coronary artery disease and a LVEF >40%
--	---

3.1.1 Efficacy

The relative risk reduction (RRR) in the primary composite outcome of CV death or HF hospitalization was 18% ($p = 0.0001$); the reduction in CV death (or all-cause death) was not significant, but the RRR in HF hospitalization was 26%. The absolute risk reduction (ARR) in the primary composite mortality – morbidity endpoint was 4.2%, equating to a number needed to treat (NNT) (for an average of 23 months to postpone one event) of 24. Ivabradine also improved LV function and quality of life.

3.1.2 Safety Concerns

3.1.2.1 Overall Safety

The safety profile of ivabradine was assessed in 6,558 subjects and /or patients with CHF with an average age of 60.7 years in SHIFT. The average exposure of all patients in the ivabradine group ($n = 3,232$) was 20.0 ± 9.0 months with 79% ($n = 2,548$ patients) exposed for at least 1 year and 35% ($n = 1,141$) for at least 2 years. Sixty-seven percent of patients received 7.5 mg ivabradine BID, 24% received 5 mg ivabradine BID, and 9% received 2.5 mg ivabradine BID. During the pre-midcycle meeting clinical reviewers identified atrial fibrillation (AF), bradycardia, and atrioventricular (AV) block as safety concerns. The most recent clinical review identified bradycardia as ivabradine's principle toxicity.

The most common serious adverse events in the SHIFT trial included bradycardia (4.6%), AF (8.3%), and AV block (0.2%). Bradycardia was reported within the first 2 to 3 months of treatment initiation by 0.4% of subjects. In addition, luminous phenomena (phosphenes) was a common non-serious adverse event (AE) occurring in 2.8% of subjects in SHIFT. Phosphenes were a dose dependent event and were considered transient and mild to moderate in intensity. Patients recovered during or after treatment and <1% of patients discontinued treatment or changed their daily activities due to phosphenes. Due to the non-serious, transient and non-permanent nature of this AE, phosphenes will not be addressed further in this review.

In addition, clinical reviewers also identified the potential risk of acute renal failure (ARF). The reviewers hypothesized that subjects with heart failure are at risk for renal failure from ivabradine because their cardiac output is more dependent on heart rate given their reduced stroke volumes. The clinical reviewers requested that the Sponsor explore this safety concern in-depth. On December 19, 2014, the Sponsor submitted a response to the information request. The Sponsor communicated that ivabradine does not appear to be associated with an increased risk of renal failure. This conclusion applies to the overall SHIFT population, which is representative of the heart failure population targeted in ivabradine's proposed indication statement as well as in potentially more vulnerable subgroups including patients with low baseline estimated glomerular filtration rate (eGFR), left ventricular ejection fraction, heart rate, or systolic blood pressure or those patients with low heart rates or a large reduction in heart rate from baseline after

ivabradine initiation. The Sponsor also noted that the risk of ARF does not appear to be increased in ivabradine subgroups with low heart rate or a low ejection fraction. The Sponsor concluded that it is unlikely that ivabradine-induced AF would represent a precipitating factor for acute renal failure. The clinical reviewer concurred with this conclusion based on the relatively low frequency of cases observed.

In addition, teratogenicity was observed in pre-clinical animal studies. This was identified as a potential safety concern during the clinical review and will be discussed below. The safety concerns observed during clinical trials in humans (AF, bradycardia, and AV block) will also be discussed in detail below.

As noted in the introduction, this product has been approved for use in Europe since October 2005. Thus, there is a large database for ivabradine use in the post-marketing setting demonstrating an overall positive safety profile.

3.1.2.2 Atrial fibrillation

The clinical reviewers reported that AF was one of the most common, serious adverse events leading to drug discontinuation. AF was also an adverse event requiring added therapy where the rates were higher for the ivabradine versus placebo group. According to the clinical reviewers, AF occurred more frequently in ivabradine treated subjects (20% higher). AF was considered an important potential risk during the BEAUTIFUL trial for the indication of stable angina. AF was also identified as a safety concern during the SHIFT clinical trial. Overall, in SHIFT, AF was higher in the ivabradine group than in the placebo group: 8.2% (4.9% patient-years) versus 6.6% (3.9% patient-years) respectively. In the ivabradine group, 3.6% of the cases were assessed as serious by the investigators versus 3.2% in the placebo group. In addition, in the SHIFT trial, the incidence of AF for the CHF indication was noticeably higher than observed in the population for the angina indication. The cases reported in SHIFT recovered in a similar proportion in the two groups (64% and 65%, respectively). Overall, the rates of death were similar between the ivabradine (n= 512, 8.6% patient years) and the placebo (n= 563, 9.5% patient years) groups in SHIFT. However, AF was the most common adverse event (4.2%) resulting in treatment withdrawal.

The higher incidence of AF observed in both treatment groups (ivabradine and placebo) in the SHIFT study may be explained by the characteristics of the selected population, as it is understood that AF and CHF frequently co-exist, partly because of common risk factors. In the SHIFT study, ivabradine-treated patients who experienced AF tended to be older (mean age 64.3 years), either in NYHA class III or IV, and to have a previous history of AF (approximately 25% of these patients) than in the overall population of the SHIFT study.

Nonetheless, the clinical reviewer reported that ivabradine appears to be causing an increase of AF. The overall absolute incremental AF risk in SHIFT was approximately 1.7% (relative increase versus placebo = 25%). Consequently, there were more patients with AF adverse events in SHIFT's ivabradine treatment group compared to placebo (306 versus 251, respectively). Also, all six cases of TEAE sick sinus syndrome during the SHIFT treatment period occurred in the ivabradine treatment group. In SHIFT, AF was serious in nearly half of subjects with an event and had a fatal outcome in 1 subject on

ivabradine (described above). In SIGNIFY, the absolute increase in AF in the subgroup of patients with angina was 1.4% (relative increase versus placebo = 44%).

In conclusion, the SHIFT study had more frequent AF reports with ivabradine than with placebo. However, these events did not result in serious outcomes in most cases for both the test and placebo groups. Nonetheless, the safety reviewer believes that ivabradine may contribute to the incidence of AF in patients taking ivabradine. The safety reviewer believes that ivabradine should not be used in patients with permanent AF. The CDTL reviewer concluded that AF was a manageable AE.

3.1.2.3 Bradycardia

The clinical reviewers reported that there was a higher risk of bradycardia as a serious AE compared to placebo (~4-5X higher). During SHIFT, 5.0% of patients on ivabradine had symptomatic bradycardia compared with 1% of the placebo group (p = 0.0001). Incidence of bradycardia reported as an AE in BEAUTIFUL was 3.3% (0.72% patient-months, i.e. 8.6 patients-years) on ivabradine 5-7.5 mg BID versus 1.0% (0.39% patient-months, i.e. 4.7% patient-years) on placebo. It occurred particularly within the first 2 to 3 months of treatment initiation.

Comparison of the incidence of bradycardia between ivabradine and placebo in CHF patients in BEAUTIFUL, SHIFT, and SIGNIFY demonstrated the following incidence: 9.7% (6.1% patient-years) versus 2.2% (1.3% patient-years) with more frequent asymptomatic bradycardia (5.6% of the patients [3.5% patient-years] in the ivabradine group versus 1.4% [0.8% patient-years] in the placebo group) than symptomatic bradycardia (4.4% [2.8% patient-years] in the ivabradine group versus 0.9% [0.5% patient-years] in the placebo group). Event characteristics in this pooled population of clinical trial subjects were: rarely serious (0.4%), leading to study drug discontinuation in few cases (0.6% SHIFT; 0.5% BEAUTIFUL) and resolved in the large majority of cases (96%). No reported cases were fatal. Thus, the cases of bradycardia were common, but the outcomes were usually not serious.

The clinical reviewer noted that ivabradine has no more risk of bradycardia than many common medications used in CHF patients including metoprolol (incidence of bradycardia = ~1.5% (HR < 40 bpm) [*see Prescribing Information - Adverse Reactions*]) or verapamil (incidence of bradycardia (HR < 50 bpm) = 1.4% [*see Prescribing Information - Section 6.1 Clinical Trials Experience*]). These medications are currently marketed without a REMS program and have decades of cumulative safety data to support their use in patients with CHF NYHA Class II to IV. In addition, the CDTL reviewer commented that reduced heart rate is an expected pharmacologic action of ivabradine. The clinical reviewer recommended that the labeling and instructions to physicians should communicate these concerns clearly.

3.1.2.4 Atrioventricular Block

AV block II and III were non-inclusion criteria in both the BEAUTIFUL and SHIFT trials. Incidences of AV block reported as adverse events in the SHIFT safety data set were, for AV block I: 1.4% (0.3% patient-months, i.e. 3.6% patient-years) on ivabradine (5 to 7.5 mg BID) versus 1.0% (0.4% patient-months i.e. 4.8% patient-years) on placebo; for AV block II: 0.1% (0.03% patient-months i.e. 0.4% patient-years) on ivabradine

versus none on placebo; for AV block III: none in both treatment groups. One case of AVB II with ivabradine was considered as serious; one AV block II case was not resolved. In addition, one case of AV block of unspecified degree was reported in the ivabradine group (not serious and not leading to study drug discontinuation, not recovered).

It should be noted that almost all the cases of AV block II and AV block III occurred in the SHIFT study. Patients experiencing AV block II/III tended to be older, to have slightly more severe left ventricular dysfunction and were more likely to have a background history of conduction disorders (left bundle branch block (LBBB), bifascicular block, AV block I). In the ivabradine group, one patient had experienced a previous episode of complete AV block before entering the trial and in 2 patients, the event occurred during the course of an acute myocardial infarction.

The clinical reviewer noted that ivabradine has no more risk of AV block than many common medications used in CHF patients including metoprolol (incidence of AV block I (PR \geq 0.26 sec) = 3.4% [Adverse reactions section of approved labeling]) or verapamil (incidence of AV block I = 0.4% [Adverse reactions section of approved labeling]). These medications are currently marketed without a REMS program and have decades of cumulative safety data to support their use in patients with chronic heart failure NYHA Class II to IV.

3.1.2.5 Teratogenicity

The Pharmacology/Toxicology (Pharm/Tox) reviewer reported that preclinical data clearly show that ivabradine is a teratogen that causes malformations in the heart. Ivabradine was shown to cause heart malformations in rats and reduced embryo-fetal survival in rats at exposures close to the recommended therapeutic dose. These pregnant animals received ivabradine during organogenesis. The abnormalities observed included abnormal heart shape with anomalies of the major proximal arteries in the rats. Juvenile rats studied also demonstrated similar toxicological profiles with the heart being the target organ. Ivabradine was also associated with ectrodactylia in rabbits at exposures 15 to 34 times the human dose. The Pharm/Tox reviewer noted that ectrodactylia occurred in one fetus each of the control group and the treated group. However, the control subject had multiple additional defects and amniotic bands whereas the treated subject had no other defects. It is not clear whether these cases were definitive. Therefore, no firm conclusion can be drawn regarding the potential teratogenic effect observed in the pivotal rabbit study.

During clinical trials in humans, 3 subjects exposed to ivabradine became pregnant. One subject elected to terminate the pregnancy and the other subjects (total cumulative doses = 50mg and 30mg) had full-term pregnancies with no identified dysmorphic features. During post-marketing surveillance (2005 to April 2014) there were a total of 21 patients exposed to ivabradine during their first trimester of pregnancy. The outcomes are listed below in Table 2.

<u>n</u>	<u>Outcome</u>
2	Terminated pregnancy
3	Ongoing pregnancy at data lock point
7	Lost to follow-up
9	Live births <ul style="list-style-type: none"> • 7 full-term births • 2 premature births

Table 2. List of post-marketing patients (n = 21 cases) receiving ivabradine during pregnancy.

All 9 live births were for normal babies without any signs of dysmorphic features. The premature births (Table 2) involved the following complications: The first case involved growth retardation. The delivery was induced due to harmonious in-utero fetal growth retardation at 37.7 weeks of amenorrhea. The birth parameters were a weight of 2510 g, a height of 46 cm, and a cranial perimeter of 30.5 cm. The mother suffered from aortic valvular insufficiency, Marfan’s syndrome, and was a smoker. She was also taking metoprolol, aspirin, enoxaparin, and pantoprazole. The second case of premature birth involved growth restriction. At 34 weeks of pregnancy biometric fetal parameters were not growing. A caesarean section was performed at (b) (6) weeks and the birth weight was 2120 g. No malformations were reported.

It is important to note that ivabradine has been marketed in Europe since 2005. In the European labeling, ivabradine is contraindicated in women of child-bearing potential who are not using appropriate contraceptive measures. The clinical reviewers recommended that ivabradine should not be used in women of child-bearing potential who are not using appropriate contraception.

As a response to an Agency information request (eCTD Seq. No. 61), the Sponsor submitted additional information related to ivabradine exposure in pregnant women and pregnancy outcomes. The Sponsor reports that there was a total of 24 pregnancies worldwide with exposure to ivabradine. Three of these were previously reported in clinical trials (above). The data collected was from the European Union and ranged from October 25, 2005 to April 25, 2014. The trimester of exposure of ivabradine is as follows: 1st trimester (16), through 2nd trimester (2), through 3rd trimester (1), unknown (1), and in 1 case, the patient was treated with ivabradine since an unknown date and stopped the product when she was (b) (6) weeks pregnant.

Of the 21 post-marketing ivabradine exposures, 7 cases were lost to follow up and no information was obtained on the delivery. However, in one of these cases, a normal ultrasound on the 22nd week of pregnancy was reported. Among the remaining 14 cases, 9 led to spontaneous delivery without abnormalities (including 2 deliveries with fetal growth retardation/restriction), and 2 were induced abortions. Three pregnancies were still on-going at the data lock point (25 April 2014). The 2 cases of fetal growth retardation are detailed above. The cases detailed here provide evidence of potential fetal

growth retardation and other congenital abnormalities when pregnant women are exposed to ivabradine.

4 SUMMARY OF SPONSOR'S PROPOSED LABELING FOR IVABRADINE

Safety Concern of Interest	Proposed Labeling Sections
AF	<ul style="list-style-type: none"> • 5.0 Warnings and Precautions <ul style="list-style-type: none"> ○ 5.2 Increased risk of AF • 6.0 Adverse Reactions <ul style="list-style-type: none"> ○ 6.1 Clinical Trials Experience
Bradycardia	<ul style="list-style-type: none"> • 5.0 Warnings and Precautions <ul style="list-style-type: none"> ○ 5.3 Bradycardia • 6.0 Adverse Reactions <ul style="list-style-type: none"> ○ 6.1 Clinical Trials Experience • 7.0 Drug Interactions • 10.0 Overdosage
AV Block	<ul style="list-style-type: none"> • 4.0 Contraindications • 6.0 Adverse Reactions <ul style="list-style-type: none"> ○ 6.1 Clinical Trials Experience
Teratogenicity	<ul style="list-style-type: none"> • 5.0 Warning and Precautions <ul style="list-style-type: none"> ○ 5.1 Fetal Toxicity • 8.0 Use in Specific Populations <ul style="list-style-type: none"> ○ 8.1 Pregnancy

Table 3. Summary of safety concerns and Sponsor's proposed labeling. The Sponsor's proposed labeling (submitted September 2014) has not been finalized with the Agency

5 DISCUSSION

Ivabradine was shown to be efficacious and decreased the composite endpoint of CV death and CHF hospitalizations during clinical trials. If approved it will be the first new class of drug approved in over a decade for CHF, a chronic life threatening disease which affects about 5.1 million patients in the US. The benefits in the indicated patient population are significant.

Ivabradine is a new molecular entity with a unique mechanism of action. However, the safety profile of this medication is not unique as compared with other medications indicated in the treatment of chronic heart failure patients (i.e., metoprolol and verapamil). Based on the currently available data, the risk of bradycardia, AF, or AV block is comparable to other commonly used drugs used for CHF which do not have any risk mitigation beyond labeling.

The proposed indication for ivabradine will include patients with stable, symptomatic chronic heart failure with a LVEF \leq 35 % and in sinus rhythm with resting heart rate \geq (b) (4) b.p.m., who are taking optimal doses of standard heart failure therapies including beta blockers, or when beta blocker therapy is contraindicated (b) (4). The standard of care for the indicated patient population may involve healthcare providers consisting of cardiologists, primary care physicians, and nursing staff that have experience treating this patient population, therefore, do not need additional training to identify or manage the potential serious adverse events associated with ivabradine. Also, since this medication is indicated for the treatment of a chronic condition the standard of care is for HCPs to routinely follow up and consistently monitor a patient's health status while using ivabradine. The routine follow up will improve the HCPs ability to detect any potential adverse events. Finally, if approved ivabradine will be used in patients (b) (4)

(b) (4) have failed beta blocker therapy with the potential concomitant use of ACE inhibitors, diuretics, or mineralocorticoid antagonists. These patients should have an existing, well-developed therapeutic monitoring regimen to identify risks associated with their treatment including those potentially associated with ivabradine; such as, bradycardia, AF, and AV block.

Considering the risk of teratogenicity in the completed animal studies, the Pharm/Tox reviewer considers ivabradine a potential teratogenic in humans.² Additionally, the Cross-Discipline Team Leader (CDTL) Review Memo³ identified teratogenicity as a special safety concern. However, clinical and post-marketing data show no cases demonstrating teratogenic effects in the 24 recorded ivabradine pregnancy exposure cases. The Sponsor submitted a summary of the world-wide experience (see section 3.1.2.5) with ivabradine exposure in pregnant women with regard to pregnancy outcomes (i.e., abortion, congenital abnormalities, fetal toxicity, and teratogenicity). Currently, the warning of teratogenicity will be included in the *Warnings and Precautions* section and *Use in Specific Populations* section of the label. The Agency has requested revised labeling based on the new Pregnancy and Lactation Labeling Rule. Overall, the clinical reviewer believes that ACE inhibitors have similar risks of teratogenicity as ivabradine. In addition, if approved, the Sponsor will introduce the existing international Pregnancy Surveillance Program in the US to detect teratogenicity.

The Sponsor has proposed a Medication Guide (MG) (eCTD Seq. No. 0067) for ivabradine. The current, proposed MG addresses the risks of bradycardia, AF, and luminous visual phenomena/phosphenes. DRISK agrees with the proposal to have a MG and recommends the inclusion of risk messages to inform patients of the risks of ivabradine to the fetus if they become pregnant. The MG will be reviewed by the Patient Labeling Team (PLT) when substantially complete labeling is available.

The use of a REMS program to mitigate the risk of teratogenicity is not necessary to ensure the benefits outweigh the risk of teratogenicity. Appropriate labeling should mitigate the risk of teratogenic effects in patients by informing HCPs of the risk since cardiologists and primary care physicians, who routinely prescribe ACE inhibitors and ARBs, are familiar with the risk of teratogenicity and labeling for teratogenicity in other products used to treat this patient population. In addition, DRISK recommends a MG to address teratogenicity to inform patients of this risk. Furthermore, the Sponsor's proposed Pregnancy Surveillance Program will assist in the tracking of pregnancies and teratogenicity in a post-marketing setting. For the risks discussed above (i.e., bradycardia, AF, AV block, and teratogenicity) after considering the indicated patient's predisposition to these risks, the use of labeling to mitigate similar risks in drugs (i.e., metoprolol, verapamil, ACE inhibitors and ARB) used for this indication, and the prescribers' experience managing these very complex and fragile patients, a REMS program is not necessary for the benefits to outweigh the risks of ivabradine use. In addition, the

² For complete details on the rationale supporting this decision please refer to the Pharmacology/Toxicology Review, dated November 2014.

³ For complete details on the rationale supporting this decision please refer to CDTL Review, dated December 8, 2014.

combination of extensive post-marketing data available for ivabradine along with the likely prescriber's awareness of these risks and their experience managing them in this patient population make a REMS program unnecessary for the benefits to outweigh the risks of ivabradine use.

6 CONCLUSION

In conclusion, based on the available data, the Office of Surveillance and Epidemiology (OSE), DRISK recommends that ivabradine, if approved, does not require a REMS to ensure the benefits outweigh the risk.

7 RECOMMENDATIONS

The OSE, DRISK does not recommend that ivabradine have a REMS program for approval. Comprehensive labeling and a MG discussing the risks associated with ivabradine use will ensure that the benefits outweigh the risks of ivabradine.

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

/s/

DANNY S GONZALEZ
03/02/2015

REEMA J MEHTA
03/03/2015
I concur.