EU RISK MANAGEMENT PLAN FOR RANEXA® (RANOLAZINE)

RMP version to be assessed as part of this application:

RMP Version number: 8.2

Data lock point for this RMP: 26 January 2018

Date of final sign off: 03 September 2018

Rationale for submitting an updated RMP:
The RMP has been updated according to the PRAC Rapporteur's updated assessment report, issued on 22 August 2018, in the frame of the assessment of PSUSA Procedure n. EMEA/H/C/PSUSA/00002611/201801 of the EU PSUR#10 with covered period 27 January 2015_ 26 January 2018.
The RMP version 8.1 has been submitted within the above mentioned procedure in order to include a number of modifications, as listed in the Request for Supplementary Information of the PRAC Rapporteur's preliminary assessment report related to the RMP version 8.0.
Following the outcome of such assessment, the PRAC rapporteur is requiring a number of modifications, as listed in the conclusions and actions of the PRAC Rapporteur's updated assessment report.

Summary of significant changes in this RMP:
The following changes of the safety issues have been performed:
- According to the PRAC Rapporteur's updated assessment report (Procedure n. EMEA/H/C/PSUSA/00002611/201801), the list of safety concerns has been updated (the safety concern "QT prolongation" has been restored as an Important Identified Risk) and the concerning sections have been aligned accordingly.

Other RMP versions under evaluation:

RMP Version number: 8.1

Submitted on: 02 August 2018

Procedure number: EMEA/H/C/PSUSA/00002611/201801

Details of the currently approved RMP:

Version number: 7.2

Approved with procedure: EMEA/H/C/805/PSU 018

Date of approval (opinion date): 13 November 2013

QPPV name: Dr. Francesco Sar[redacted]MD

QPPV signature: [redacted]

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Not applicable

LIST OF ABBREVIATIONS

ACCF-AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin Converting Enzyme
AChR	Acetylcholine Receptor
ADRs	Adverse Drug Reactions
AEs	Adverse Events
AESI	Atrial Extra Systolic Interval
AF	Atrial Fibrillation
AHA	American Heart Association
AP	Angina Pectoris
APC	Adenomatous Polyposis Coli
ARIC	Atherosclerotic Risk in Communities
ATP	Adenosine Triphosphate
AV	Atrioventricular
AUC	Area Under the Curve
BID	Bis In Die
BMI	Body Mass Index
BP	Blood Pressure
Cmax	Maximum Concentration
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CHS	Cardiovascular Health Study
CVD	CardioVascular Disease
CVT	Continuous Variable Trasmission
CV	Cardiovascular Event
CVT	Cerebral Vein and Thrombosis
CYP	Cytochromes P450
CYP2D6	Cytochrome2D6
CYP3A4	Cytochrome3A4
DHP	Dihydropyridine
DLP	Data Lock Point
EEA	European Economic Area
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
EU	European Union

EURD	European Union Reference Date
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GP	Glycoprotein
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
ISD	Integrated Safety Database
LEMS	Lambert-Eaton Myasthenic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST Elevation Myocardial Infarction
NYHA	New York Heart Association
OTC2	Organic Cation Transporter 2
PCI	Percutaneous Coronary Intervention
P-gp	P-glycoprotein
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PR	Prolonged Release
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUFA	Polyunsaturated Fatty Acids
QTcB	QT Bazett's correction
QTcF	QT Fridericia correction
RMP	Risk Management Plan
RR	Reporting Rate
SAEs	Serious Adverse Events
SCAD	Spontaneous Coronary Artery Dissection
SmPC	Summary of Product Characteristics
SVT	Sustained Ventricula Tachycardia
TdP	Torsades de Pointes
UA/NSTEMI	Unstable Angina and Non–ST-segment Elevation Myocardial Infarction
UK	United Kingdom
US	United States
VT	Ventricular Tachycardia

PART I. PRODUCT(S) OVERVIEW

Table Part I–1 – Product Overview

Active substance(s) (INN or common name)	Ranolazine
Pharmacotherapeutic group(s) (ATC Code)	Other cardiac preparations (ATC code:C01EB18)
Marketing Authorisation Holder/Applicant	Menarini International Operations Luxembourg S.A
Medicinal products to which this RMP refers	Ranolazine 375 mg prolonged-release tablets Ranolazine 500 mg prolonged-release tablets Ranolazine 750 mg prolonged-release tablets EU/1/08/462/001 EU/1/08/462/002 EU/1/08/462/003 EU/1/08/462/004 EU/1/08/462/005 EU/1/08/462/006 EU/1/08/462/007 EU/1/08/462/008 EU/1/08/462/009 EU/1/08/462/010 EU/1/08/462/011 EU/1/08/462/012
Invented name(s) in the European Economic Area (EEA)	Ranexa
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Ranolazine is an acetanilide and piperazine derivative.
	Summary of mode of action: Ranolazine may have some antianginal effects by inhibition of the late sodium current in cardiac cells. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intracellular ionic imbalances during ischaemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness.
	Important information about its composition: The active ingredient is obtained by chemical synthesis.
Hyperlink to the Product Information	SmPC of Ranolazine 375 mg prolonged-release tablets SmPC of Ranolazine 500 mg prolonged-release tablets SmPC of Ranolazine 750 mg prolonged-release tablets PL of Ranolazine 375 mg , 500 mg and 750 mg prolonged-release tablets

Indication(s) in the EEA	Current: Ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended initial dose of ranolazine in adults is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily. If a patient experiences treatment-related adverse events (e.g. dizziness, nausea, or vomiting), down-titration of ranolazine to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 375 mg prolonged-release tablets 500 mg prolonged-release tablets 750 mg prolonged-release tablets
	Proposed : Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

PART II: MODULE SI. - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication:

Ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

Incidence:

Women have a similarly high incidence of stable angina compared with men.
Furthermore, stable angina in women is associated with increased coronary mortality relative to women in the general population and, among easily identifiable clinical subgroups, has similarly high absolute rates of prognostic outcomes compared with men (Hemingway et al., 2006).
Only 18% of coronary attacks are preceded by longstanding angina pectoris.
The annual rates per 1000 population of new episodes of angina pectoris for nonblack men are 28.3 for those 65 to 74 years of age, 36.3 for those 75 to 84 years of age, and 33.0 for those ≥85 years of age.
For nonblack women in the same age groups, the rates are 14.1, 20.0, and 22.9, respectively.
For black men, the rates are 22.4, 33.8, and 39.5, and for black women, the rates are 15.3, 23.6, and 35.9, respectively (CHS, NHLBI).
On the basis of 1987 to 2001 data from the ARIC study of the NHLBI, the annual rates per 1000 population of new episodes of angina pectoris for nonblack men are 8.5 for those 45 to 54 years of age, 11.9 for those 55 to 64 years of age, and 13.7 for those 65 to 74 years of age.
For nonblack women in the same age groups, the rates are 10.6, 11.2, and 13.1, respectively.
For black men, the rates are 11.8, 10.6, and 8.8, and for black women, the rates are 20.8, 19.3, and 10.0, respectively (National Heart, Lung, and Blood Institute. Incidence and Prevalence: 2006 in Heart Disease and Stroke Statistics- 2011 Update: A Report from the American heart Association).

Prevalence:

Although coronary heart disease (CHD) mortality rate has steadily declined since its peak in the 1960s, morbidity from CHD has shown opposite trends, with increasing rates of revascularisation and an increasing prevalence of angina pectoris. Stable angina pectoris affects up to 5% of the adult population over the age of 40 in most developed countries (Barbero U et al, 2016). Approximately 9.8 million Americans alone are estimated to experience angina annually, with 500,000 new cases of angina occurring every year (Alaeddini J, 2017). Age-adjusted prevalence rates for angina in the United States are higher among women than men (Bittner V, 2008). Angina symptoms tend to persist despite medical therapy and revascularization, leading to substantial functional disability and association with high healthcare costs even in the absence of obstructive coronary artery disease (CAD) (Bittner V, 2008).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The prevalence of angina in population-based studies increases with age in both sexes, from 5–7% in women aged 45–64 years to 10–12% in women aged 65–84 and from 4–7% in men aged 45–64 years to 12–14% in men aged 65–84. Interestingly, angina is more prevalent in middle-aged women than in men, probably due to the higher prevalence of functional CAD—such as microvascular angina—in women whereas the opposite is true in the elderly. (ESC Guidelines on the management of stable coronary artery disease 2013). A study of 4 national cross-sectional health examination studies found that among Americans 40 to 74 years of age, the age-adjusted prevalence of angina pectoris was higher among women than men. Increases in the prevalence of AP occurred for Mexican American men and women and African American women but were not statistically significant for the latter (Heart Disease and Stroke Statistics- 2011 Update: A Report from the American heart Association).
Available data suggest an annual incidence of uncomplicated angina pectoris of 1.0% in male western populations aged 45–65 years, with a slightly higher incidence in women under the age of 65 (ESC Guidelines on the management of stable coronary artery disease 2013).

The main existing treatment options:

According to the most updated international guidelines the two aims of the pharmacological management of stable coronary artery disease are to obtain symptom's relief and to prevent CV events (ESC guidelines on the management of SCAD 2013, AHA guidelines 2012, NICE guidelines last update 2016). The prevention of death or myocardial infarction should be pursued through pharmacological or lifestyle interventions aimed to reduce plaque progression and to stabilize the plaque avoiding thrombosis as well.
More specifically, the management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy and patient education: smoking is a strong and independent risk factor for CVD and all smoking, including environmental smoking exposure, must be avoided in all patients with CVD (ESC guidelines 2013).
A healthy diet and physical activity reduce CVD risk; energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight that is, a BMI < 25 kg/m^2. Current recommendations are to increase PUFA intake through fish consumption, rather than from supplements (ESC guidelines 2013).
As regard with pharmacological management of stable CAD, rapidly acting formulations of nitroglycerin are able to provide immediate relief of the angina symptoms once the episode has started or when the symptom is likely to occur (immediate treatment or prevention of angina).
Anti-ischaemic drugs and revascularization all have a role to play in minimizing or eradicating symptoms over the long term (long-term prevention).
In patients with severe lesions in coronary arteries supplying a large area of jeopardized myocardium, a combined pharmacological and revascularization strategy offers additional opportunities for improving prognosis by improving heart perfusion or providing alternative perfusion routes (ESC guidelines 2013).
NICE recommends revascularisation (by CABG) for patients who have left main stem and/or proximal 3-vessel disease (Archbold, 2016).

β-blockers act directly on the heart to reduce heart rate, contractility, atrioventricular (AV) conduction and ectopic activity. Additionally, they may increase perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas.
In post-MI patients, β-blockers achieved a 30% risk reduction for CV death and MI.
Calcium antagonists (i.e. CCBs) act chiefly by vasodilation and reduction of the peripheral vascular resistance. CCBs are a heterogeneous group of drugs that can chemically be classified into the DHPs and the non-DHPs, their common pharmacological property being selective inhibition of L-channel opening in vascular smooth muscle and in the myocardium (ESC guidelines 2013).
Antiplatelet agents decrease platelet aggregation and may prevent formation of coronary thrombus. Due to a favourable ratio between benefit and risk in patients with stable CAD and its low cost, low-dose aspirin is the drug of choice in most cases and clopidogrel may be considered for some patients. The use of antiplatelet agents is associated with a higher bleeding risk.
P2Y12 receptor inhibitor therapy is an important component of antiplatelet therapy in patients with UA/NSTEMI and has been tested in several large trial populations with UA/NSTEMI (ACCF-AHA Guidelines 2012).
The FDA approved the use of prasugrel and ticagrelor based on data from head-to-head comparison trials with clopidogrel, in which prasugrel and ticagrelor were respectively superior to clopidogrel in reducing clinical events but at the expense of an increased risk of bleeding.
The efficacy of glycoprotein (GP) IIb/IIIa inhibitor therapy has been well established during PCI procedures and in patients with UA/NSTEMI, particularly among high-risk patients such as those with elevated troponin biomarkers, those with diabetes, and those undergoing revascularization (ACCF-AHA Guidelines 2012).
In addition, angiotensin converting enzyme inhibitors reduce total mortality, MI, stroke and heart failure among specific subgroups of patients, including those with heart failure, previous vascular disease alone, or high-risk diabetes (ESC guidelines 2013).
Use of β-blockers and/or calcium channel blockers as first-line antianginal therapy, with long-acting nitrates, ivabradine, nicorandil or ranolazine reserved for patients who have contraindications to these agents or who fail to tolerate them is also recommended by NICE (Archbold, 2016).
Coronary revascularisation is one option for patients with significant obstructive coronary artery stenosis, with large areas of ischemia induced by stenosis and for those patients whose symptoms are not responsive to medical therapy (ESC guidelines 2013).
The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, the amount of related ischaemia and the expected benefit to prognosis and/or symptoms (ACCF-AHA Guidelines 2012).
NICE recommends that men and women with symptoms of stable angina should be investigated and treated no differently; NICE recommends a target blood pressure of <140/90 mm Hg in patients aged <80 years and <150/ 90 mm Hg in those aged >80 years. The ESC recommends lowering blood pressure to <140/90 mm Hg irrespective of age, and to <140/85 mm Hg in patients with diabetes (Archbold, 2016).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Stable angina is the most common manifestation of coronary heart disease. While considered relatively benign in terms of prognosis, the condition confers a higher risk of cardiovascular events than in the general population, with average annual mortality rates of 1–2% (Lopez-Sendon et al, 2012). Development of angina, particularly where the angina is unstable and the heart is not receiving enough blood flow and oxygen is a serious warning sign of increased risk of heart attack, cardiac arrest, arrhythmias, sudden cardiac death as well as stroke. Medical intervention is therefore always appropriate due to the life threatening nature of this condition. Living with a long-term condition such as angina can also have a great impact on emotional wellbeing, with anxiety and depression as common symptoms.

Important co-morbidities:

Angina pectoris is usually equated with underlying obstructive CAD and other risk factors including hypertension, smoking, diabetes mellitus, obesity and hyperlipidaemia (Alaeddini J, 2017). Family history of coronary artery disease is also an important risk factor as well as age (men older than 45 and women older than 55 have a greater risk), lack of exercise, obesity and stress with associated high cholesterol and blood pressure (Boudi FB et al, 2016).

PART II: MODULE SII. **- NON-CLINICAL PART OF THE SAFETY SPECIFICATION**

The nonclinical safety program for ranolazine was conducted to focus specifically on the toxicological properties of ranolazine and the systemic effects from dose related exposure.

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies

In single dose toxicity studies mortalities were observed in rats and mice at 250 mg/kg os, and in dogs at 150 mg/kg os or 40 mg/kg i.v. In all species deaths were associated with convulsions, collapse, ataxia, and subdued behaviour (Module 2.4 Nonclinical overview; Section 2.4.5.1). The maximum non-lethal doses were 50 mg/kg os and 30 mg/kg i.v. in mice, <250 mg/kg os and 30 mg/kg i.v. in rats, 100 mg/kg os and 20 mg/kg i.v. in dogs. In mice single dose Cmax values at 50 mg/kg os were respectively 6.7 and 5.2 µg/mL in males and females, whereas, for rats and dogs, Cmax values were available only for doses lower than the maximum non-lethal doses. In rats dosed orally at 150 mg/kg Cmax values were 14.2 and 15.6 µg/mL in males and females, respectively, whereas in dogs dosed orally at 60 mg/kg the Cmax values were 9.0 and 8.9 µg/mL in males and females, respectively (Module 2.6.4, Sections 3.1 and 3.2). Considering that in humans dosed with 1000 mg twice daily the mean Cmax is 1.7 µg/mL and the AUC is 18.3 µg*h/mL (geometric means of the first day of treatment, see study CVT 3015), the safety margins before achieving toxicity are quite wide.

Two repeat-dose toxicity studies in mice designed to select dosages for carcinogenicity testing were performed. The first study, which scheduled the administration of 0, 5, 50, 100 and 200 mg/kg/day, p.o. for 13 weeks was terminated early (8^{th} day) for excess mortality at the highest doses. In the second 13-week study (0, 5, 15, 25 and 35 mg/kg/day, p.o) no evidence of toxicity was provided at any level of dose. There was also no evidence of toxicity in a 2-year carcinogenicity test performed in mice up to 50 mg/kg/day (Module 2.4 Nonclinical overview; Section 2.4.5.2.1). Mean ranolazine plasma levels, taken at about the Tmax, and measured following 2-year oral treatment with 50 mg/kg/day were 5.4 and 5.0 µg/mL (Module 2.6.4, Section 3.2.1).

In repeat oral dose toxicity studies performed in rats, treatment-related deaths were only observed at highest dosages: at 250 and 500 mg/kg/day in a 3-month study (AT-3465), and at 200 mg/kg in 6- and 12-month studies (AT 3935 and AT 6544, respectively). Increased mortality, particularly in males at 150 mg/kg/day, forced the premature termination of the carcinogenicity study (AT 7041) after 21 months of treatment (Module 2.4 Nonclinical overview; Section 2.4.5.2.2.1). The target organs for toxicity in surviving animals at these high doses were adrenal glands. Increased adrenal weight was also occasionally observed at lower doses, but this finding was neither consistent between genders nor across the studies. Dose-related reductions in erythrocyte numbers and in hematocrit associated with increases in mean cell hemoglobin and mean cell hemoglobin concentration were also observed, but these changes were significant at high doses only.

The systemic exposure measured following 6-month treatment with 150 mg/kg/day (a sub-lethal dose in this study) was 19.2 and 15.6 µg/mL as Cmax and 117 and 167 µg*h/mL as AUC in males and females, respectively (study AT 6811), whereas, at the end of the carcinogenicity study the highest dose devoid of major toxic effects (50 mg/kg/day) produced AUC values of 88.2 and 72.5 µg*h/mL in males and females, respectively.

In a preliminary toxicity study performed in dogs 500 or 750 mg tablets were orally administered for 4 weeks (mean doses 45 mg/kg or 68 mg/kg, respectively): there were no clinical signs, effects on body weight, food intake, ECG, clinical pathology or necropsy despite a consistent systemic exposure.
In the 3-month oral toxicity study performed in dogs (AT 3440), vomiting, salivation, subdued behaviour, trembling, ataxia and convulsions, were recorded in the highest dose group (80 mg/kg/day), whereas no convulsions were seen at 60 mg/kg/day. The weight of the adrenals was marginally increased, but there were no treatment-related findings at the macroscopic or microscopic pathological assessment. There were no effects on body weight food intake, ophtalmoscopy or ECG. At the end of treatment with 60 mg/kg/day the AUC was 37.7 and 27.4 µg*h/mL in males and females, respectively.
In the 6-month oral toxicity study performed in dogs (AT 4050), the clinical signs consistently observed at the highest dose (60 mg/kg/day) were mydriasis, glazed eyes and ptosis. At this dose small reductions in erythrocyte numbers, hematocrit and hemoglobin concentration were also observed. A reduction in testes weight and a marginal increase in adrenal weight (in both genders) were not associated with gross necropsy or histopathological findings. At the end of treatment with 60 mg/kg/day the AUC was 29.6 and 27.8 µg*h/mL in males and females, respectively.

Relevance to human usage:
In both single and repeat dose studies important toxic effects were only observed at very high doses. In all species studies carried out in rodent species (mice, rats), doses devoid of these toxic effects warranted levels of systemic exposure which were significantly greater than those obtained with a human dose (1000 mg twice a day, where the AUC was 18.3 µg*h/mL on the first day of treatment and 30.2 µg*h/mL at the steady state, see study CVT 3015) which exceeds the maximum therapeutic dose of 750 mg twice a day approved in the EU. In dog studies, the systemic exposure measured at non-lethal doses was lower than in rodents and comparable with that recorded in humans at 2000 mg/day at the steady state. However, it should be considered that in humans the AUC refers to a twice daily administration, whereas in animals ranolazine was administered once daily; furthermore the 2000 mg/day dose is larger than the maximal approved in EEA countries (1500 mg/day). No changes in the adrenal glands have been identified in humans, and no effect on the adrenocortical function was noted in human clinical trials. Therefore, it was considered that the adverse findings recorded in single and repeat dose toxicity studies carried out in mice, rats and dogs are not relevant for the clinical use of the medicinal product.

- Reproductive/developmental toxicity

Signs of maternal and embryofoetal toxicity were recorded at 400 mg/kg/day, however, ranolazine at oral doses as high as 300 mg/kg/day had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring. Oral administration of ranolazine at 200 mg/kg/day to pregnant rats during the

perinatal and postnatal period had no adverse effects on parturition or postnatal development of offspring. Ranolazine was not teratogenic following oral administration during organogenesis at doses as high as 400 mg/kg/day in rats and 150 mg/kg/day in rabbits. (Module 2.4 Nonclinical overview; Section 2.4.5.2.2.1).

Relevance to human usage:
Ranolazine has no meaningful toxicological effects on fertility, reproductive and developmental toxicity studies at a level of doses warranting a higher systemic exposure than that observed in humans. There are no reasons to speculate that the drug can exert adverse findings on human reproductive function at the clinically recommended doses, however, due to the lack of human-specific data, caution must be taken before treating pregnant and breast-feeding women. Furthermore, whether ranolazine is excreted through the milk has not been established in non-clinical studies, strengthening the above caution.

- Genotoxicity

A series of separate Ames tests, one including a yeast strain sensitive to gene conversion, were all negative, as it was a study on Chinese Hamster Ovary cells with mutated Hypoxanthine-guanine phosphoribosyltransferase. A chromosomal aberration study carried out on Chinese Hamster Ovary cells was also negative, except a positive result at one concentration after 10 but not 20 hour incubation in the presence of rat liver S9 mix; therefore this positive result was considered equivocal. All studies included relevant positive controls. In vivo, a micronucleus test performed in mice was negative up to 300 mg/kg, p.o., the highest dose tested. Two other studies were performed in rats (micronucleus and rat liver comet assay; in both studies there was no evidence of genotoxic or clastogenic effects up the highest dose tested (250 mg/kg p.o.). The weight of evidence from the genetic toxicology studies indicates that ranolazine is neither genotoxic nor clastogenic (Module 2.4 Nonclinical overview; Section 2.4.5.3).

Relevance to human usage:
The weight of evidence from the in vitro and in vivo genetic toxicology studies indicates that ranolazine is neither genotoxic nor clastogenic, therefore no such adverse effects are to be expected in humans.

- Carcinogenicity

Life span carcinogenicity studies were carried out in rats and mice. Both studies included duplicate control groups. Survival was significantly reduced in male rats treated at 150 mg/kg/day. Because of poor survival, the rat study was terminated prematurely, after 21 months of treatment, with the agreement of the Food and Drug Administration (FDA), notwithstanding this the study was considered valid because an adequate sample size was maintained, including the 150 mg/kg/day group. In this latter group, a slight increase in the incidence of adrenal, subcutaneous, thyroid and testicular tumors was recorded however this increase was judged to be within the biological variability of the spontaneous occurrence in this strain of rats. The 2-year study carried out in mice (CD-1 strain) clearly excluded any carcinogenic potential of ranolazine. In contrast, an increase of gastro-intestinal tumor incidence was described in transgenic APC(min/+) mice treated with intraperitoneal ranolazine for 30 days (Suckow MA, Gutierrez LS, Risatti CA, Wolter WR, Taylor RE,

Pollard M, Navari RM, Castellino FJ, Paoni NF. The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC(Min/+) mice. Cancer Lett. 2004 Jun 25;209(2):165-9); however several methodological criticisms have been issued on this study, including issues on the chemical purity of the drug synthesized at the Authors' institution. As a matter of fact, gastro-intestinal tumors were never observed in the above mentioned GLP studies carried out in wild type rats and mice, and the intraperitoneal route is not relevant for the human use; therefore it was finally judged that ranolazine was devoid of carcinogenic potential according to the approved use; rather recent evidence would indicate anti-tumor activity both in vitro and in vivo exerted through its primary molecula target (Driffort V, Gillet L, Bon E, Marionneau-Lambot S, Oullier T, Joulin V, Collin C, Pagès JC, Jourdan ML, Chevalier S, Bougnoux P, Le Guennec JY, Besson P, Roger S. Ranolazine inhibits NaV1.5-mediated breast cancer cell invasiveness and lung colonization. Mol Cancer. 2014 Dec 11;13:264).

Relevance to human usage:
The weight of evidence indicates that ranolazine is not carcinogenic and this finding is also in agreement with the lack of mutagenic or clastogenic effects.

Safety pharmacology

- Cardiovascular system, including potential effect on the QT interval

Cardiovascular safety pharmacology studies indicate that ranolazine blocks IKr and consequently increases the QT/QTc interval. Despite the effect of lengthening the QT/QTc interval, ranolazine lacks the proarrhythmic action typically associated with drugs that cause Torsades de Pointes (TdP). Ranolazine does not induce early after depolarizations or increase transmural dispersion of ventricular depolarization, both of which are believed to underlie the mechanisms for initiation and maintenance of TdP. Ranolazine had no effect on the respiratory or gastrointestinal systems (Module 2.4 Nonclinical overview; Sections 2.4.3 and 2.4.7).

Relevance to human usage:
The increase in QT interval has been well characterized in both animals and humans, and this effect has been considered an important identified risk and monitored through the post-marketing surveillance since the launch. The results of extensive nonclinical investigations suggest that the increase in QT interval does not indicate a potential to cause TdP or other arrhythmias, as confirmed in the post-marketing surveillance

Other toxicity-related information or data

- Impurities and Degradation Products

A series of toxicity studies were carried out in batches of ranolazine in order to qualify the impurities still present in the drug product. No degradation products have been identified in the drug product. There have been no studies of the pharmacological activity of the specified impurities other than RS-94287, which, as a metabolite of ranolazine, was investigated along

with a wide range of other metabolites for effects on sodium currents and for receptor activity (Module 2.4 Nonclinical overview; Section 2.4.6.4).

Toxicological studies with impurities including RS-88778 (Di-Ran3-pip) were carried out in a 4-week rat study where 5% RS-88778 was given to rats at 20 mg/kg/day by oral gavage. The rats were compared with rats similarly treated with pure ranolazine free base. There was no evidence of any toxicity. The remaining three specified impurities, CVT-2458, CVT-2459, and CVT-3379 were also investigated in 4-week rat toxicity studies of similar design to RS-88778, also at up to 5% of a 20 mg/kg/day dose of ranolazine free base. No toxicity was seen in any of these studies (Module 2.4 Nonclinical overview; Section 2.4.6.5).

Similar 4-week rat studies have been carried out with CVT-4795 (O-Ran3-Ran), CVT-2511(o-Cl-desmethoxyRan), and CVT-2728 (DesmethylRan) which have been identified in early production batches but are not expected to be present in any future batches of the drug substance (CVT-4795 and CVT-2511) or present at very low levels (< 0.02%, CVT-2728). One other substance, RS-88056 (Di-Ran1-pip), was also similarly tested but this compound has not been identified in the drug substance. None of these rat studies identified any significant evidence of toxicity (Module 2.4 Nonclinical overview; Section 2.4.6.5).

Relevance to human usage:
None of the impurities present in the drug substance appear to represent any particular human hazard. All, with the exception of Di-Ran3-pip, are controlled at very low concentrations in the drug substance and none showed any evidence of significant toxicity. Di-Ran3-pip is not mutagenic. There are no known degradation products and residual solvents are controlled within the established ICH limits (Module 2.4 Nonclinical overview; Section 2.4.6.6). Non-clinical data reveals no special hazard for humans based on nonclinical published studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

PART II: MODULE SIII. - **CLINICAL TRIAL EXPOSURE**

An Integrated Safety Database (ISD) that includes safety data from 71 studies conducted by Syntex/CV Therapeutic (CVT) between March 1985 and August 2006 was prepared; the included studies can be divided as follows: 15 phase 2/3 immediate release and prolonged release formulation controlled studies; 5 uncontrolled, open label, long-term, follow-up studies in patients with angina, and 51 phase 1 and clinical pharmacology studies. The ISD consisted of 3463 ranolazine patients and 1829 placebo patients. Data from an additional 16 early clinical pharmacology studies (304 subjects) were not included in the ISD because of the limited availability of disposition and exposure information.
Overall, approximately 6681 subjects have been enrolled in the ranolazine clinical program, of which approximately 3690 subjects have received ranolazine. This estimate included subjects from Gilead and Menarini-sponsored clinical trials.

Table S III–1: and Table S III–2 provide the cumulative number of subjects exposed to ranolazine, placebo or comparators in ongoing and completed clinical trials. Estimates of cumulative subject exposure are based on actual exposure data from completed studies (unblinded) and the enrollment and randomization schemes for blinded ongoing studies (eg, in a trial with a 1:1:1 distribution of subjects, the approximate subject exposure to each group would be one-third of the total number of subjects enrolled in that trial).

Table S III–1: Estimated Cumulative Subject Exposure in Gilead-Sponsored Interventional Clinical Trials with ranolazine

Treatment	Number of Subjects[a]
Ranolazine[b]	2,984
Other[c]	996
Placebo only[d]	2,054
Total number of unique subjects[e]	**5,483**

a Includes subjects and healthy volunteers in the following Gilead Sponsored Studies: CVT03041, GS-US-259-0103, GS-US-259-0107, GS-US-259-0110, GS-US-259-0116, GS-US-259-0131, GS-US-259-0133, GS-US-259-0147, GS-US-270-0101, GS-US-259-0112, GS-US-259-0113, GS-US-259-0115, GS-US-259-0135, GS-US-259-0137, GS-US-259-0143, GS-US-259-0162, GS-US-259-0165.
b A subject was counted in the "Ranolazine" group if they received ranolazine, with or without other active study drug(s).
c A subject was counted in the "Other" group if they received other active study drug(s), with or without ranolazine.
d A subject was counted in the "Placebo" group only if they received only placebo study drug.
e Includes unique number of subjects only (ie, subjects counted once regardless if they received ranolazine coadministered with other co-suspect drugs in the study).

Table S III–2: Estimated Cumulative Subject Exposure in Menarini-Sponsored Interventional Clinical Trials with ranolazine

Treatment	(Number of Subjects)[a]
Ranolazine	706
Placebo	422
Best Standard Therapy	15
Observational Arm	53
Total number of subjects treated with study drugs	**1,196**

a Includes subjects and healthy volunteers from the following Menarini Sponsored Studies: RAF-01, MEIN/10/RAN-DID/001, MEIN/10/Ran-Cad/003, MEIN/11/RAN-HCM/001, MEIN/10/RAN-DID/002, MEIN/10/RAN-PCI/005, MEIN/09/Ran-Car/01, MAKR/15/Ran-Ang/001.

Table S III–3: Duration of exposure*

Cumulative for all indications (person time)		
Duration of exposure (days)	**Patients**	**Person time (months)**
0-14	360	69.23
15- 56	741	1,104.7
57-168	929	4,727.6
169-365	1,339	16,187.93
Total person time		**22,089.46**

* This includes Gilead and Menarini studies: CVT03041, GS-US-259-0103, GS-US-259-0107, GS-US-259-0110, GS-US-259-0116, GS-US-259-0131, GS-US-259-0133, GS-US-259-0147, GS-US-270-0101, GS-US-259-0112, GS-US-259-0113, GS-US-259-0115, GS-US-259-0135, GS-US-259-0137, GS-US-259-0143, GS-US-259-0162, GS-US-259-0165, RAF-01, MEIN/10/RAN-DID/001, MEIN/11/RAN-HCM/001, MEIN/10/RAN-DID/002, MEIN/10/RAN-PCI/005, MEIN/09/Ran- Car/01, MAKR/15/Ran-Ang/001. The MEIN/10/Ran-Cad/003 study is not included in this analysis because the CSR is not yet available.

An estimate of cumulative exposure to ranolazine by age, sex, and racial group is provided in the tables below:

Table S III–4: Age group and gender*

Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
Adolescents (<16 years)	0	0	0	0
Adults (16 to 65 years)	1,523	735	13,488.23	4,000.18
Elderly people (>65 years)	622	423	6,439.64	2,603.30
Not specified°	38	21	131.60	81.67
Total	**2,183**	**1,179**	**20,059.47**	**6,685.15**

* This includes Gilead and Menarini studies: CVT03041, GS-US-259-0103, GS-US-259-0107, GS-US-259-0110, GS-US-259-0116, GS-US-259-0131, GS-US-259-0133, GS-US-259-0147, GS-US-270-0101, GS-US-259-0112, GS-US-259-0113, GS-US-259-0115, GS-US-259-0135, GS-US-259-0137, GS-US-259-0143, GS-US-259-0162, GS-US-259-0165, RAF-01, MEIN/10/RAN-DID/001, MEIN/11/RAN-HCM/001, MEIN/10/RAN-DID/002, MEIN/10/RAN-PCI/005, MEIN/09/Ran-Car/01, MAKR/15/Ran-Ang/001. The MEIN/10/Ran-Cad/003 study is not included in this analysis because the CSR is not yet available.

° Data reported from MEIN/10/RAN-DID/002 and MEIN/11/RAN-HCM/001 studies. The age was not specified. The first study reported that the mean age was 65.5 ± 8.74 and the second study reported that subjects were 20-78 years old.

Table S III–5: Ethnic origin*

Ethnic origin	Patients	Person time (months)
White	2,938	24,347.97
Black	159	879.64
Asian	156	555.21
American Indian or Alaska native	1	0.07
Native Hawaiian Or Other Pacific Islander	3	20.57
Other	45	501.01
Not permitted	23	331.10
Hispanic	4	4.04
Not reported°	33	105
Total	**3,362**	**26,744.61**

* This includes Gilead and Menarini studies: CVT03041, GS-US-259-0103, GS-US-259-0107, GS-US-259-0110, GS-US-259-0116, GS-US-259-0131, GS-US-259-0133, GS-US-259-0147, GS-US-270-0101, GS-US-259-0112, GS-US-259-0113, GS-US-259-0115, GS-US-259-0135, GS-US-259-0137, GS-US-259-0143, GS-US-259-0162, GS-US-259-0165, RAF-01, MEIN/10/RAN-DID/001, MEIN/11/RAN-HCM/001, MEIN/10/RAN-DID/002, MEIN/10/RAN-PCI/005, MEIN/09/Ran-Car/01, MAKR/15/Ran-Ang/001. The MEIN/10/Ran-Cad/003 study is not included in this analysis because the CSR is not yet available.

° Ethnic origin was not reported in MEIN/10/RAN-DID/002 and MEIN/09/Ran-Car/01 studies.

PART II: MODULE SIV. - **POPULATIONS NOT STUDIED IN CLINICAL TRIALS**

SIV.1 **Exclusion criteria in pivotal clinical studies within the development programme**

Use in pregnant or lactating women

Reason for exclusion:
In general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy (ICH Topic E 8, General Considerations for Clinical Trials, March 1998).
Pregnant women were excluded from participation in clinical studies and the SmPC includes wording stating that there are no adequate data from the use of ranolazine in pregnant women, and that ranolazine should not be used during pregnancy unless clearly necessary. There were no lactating women in any of the clinical trials, and the SmPC states that ranolazine should not be used during lactation since it is not known whether ranolazine is excreted in human milk.

Is it considered to be included as missing information? No

Rationale:
The issue "Use in pregnant or lacting women and the paediatric population" has been addressed as missing information till RMP 8.0. In the current RMP version (8.1) it has been removed as requested by PRAC Rapporteur during the PSUSA procedure n. EMEA/H/C/PSUSA/00002611/201801.

Use in Paediatric

Reason for exclusion:
Ranolazine have not been studied in the paediatric population (< 18 years), and it is not intended for use in paediatric patients.

Is it considered to be included as missing information? No

Rationale:
The issue "Use in pregnant or lacting women and the paediatric population" has been addressed as missing information till RMP 8.0. In the current RMP version (8.1) it has been removed as requested by PRAC Rapporteur during the PSUSA procedure n. EMEA/H/C/PSUSA/00002611/201801.

Patients with moderate or severe hepatic disease

Reason for exclusion:
There are no data for patients with severe hepatic impairment. The PK of ranolazine has been evaluated in patients with mild or moderate hepatic impairment. Ranolazine AUC was

unaffected in patients with mild hepatic impairment but increased 1.8-fold in patients with moderate impairment. Dose and plasma concentration-related increases in the QTc interval (about 6 msec at 1000 mg twice daily) have been observed in patients treated with ranolazine, and the slope is higher in patients with moderate hepatic impairment. Therefore, the SmPC recommends ranolazine is contraindicated in patients with moderate or severe hepatic impairment.

Is it considered to be included as missing information? No

Rationale:
The issue "Safety information for patients with moderate and severe hepatic impairment" has been addressed as missing information till RMP 8.0. In the current RMP version (8.1) it has been removed as requested by PRAC Rapporteur during the PSUSA procedure n. EMEA/H/C/PSUSA/00002611/201801, because ranolazine is contraindicated in moderate or severe hepatic impairment, therefore, it is not expected that the product will be used in this population.

Patients with end-stage renal disease requiring dialysis

Reason for exclusion:
There are no data in patients with end-stage renal disease requiring dialysis, and limited experience was reported in patients with mild, moderate and severe renal impairment. There was a large inter-individual variability in AUC in subjects with renal impairment. The AUC of metabolites increased with decreased renal function. The AUC of one pharmacologically active ranolazine metabolite was 5-fold increased in patients with severe renal impairment. In the population pharmacokinetic analysis, a 1.2-fold increase in ranolazine exposure was estimated in subjects with moderate impairment (creatinine clearance 40 ml/min). In subjects with severe renal impairment (creatinine clearance 10–30 ml/min), a 1.3- to 1.8-fold increase in ranolazine exposure was estimated. Therefore, careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min) and ranolazine is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Is it considered to be included as missing information? No

Rationale:
The issue "Safety information for patients with severe and end stage renal disease requiring dialysis" has been addressed as missing information till RMP 8.0. In the current RMP version (8.1) it has been removed as requested by PRAC Rapporteur during the PSUSA procedure n. EMEA/H/C/PSUSA/00002611/201801, because ranolazine is contraindicated in severe renal impairment, therefore, it is not expected that the product will be used in this population.

Patients with a history of torsade de pointes (TdP)

Reason for exclusion:
Data suggest that ranolazine may exert its antianginal and anti-ischemic effects through concentration-, voltage-, and frequency-dependent inhibition of the late (i.e., sustained, persistent) sodium current and other cardiac ion channels and transporters.
This may lead to risk of changes in ECG (i.e., prolongation of QT interval corrected for rate [QTc]). The QT interval prolongation effect of ranolazine is caused by inhibition of IKr, which prolongs the ventricular action potential.
Other drugs with this potential have been associated with torsades de pointes-type arrhythmias and sudden death (Abrams et al., 2006).

Is it considered to be included as missing information? No

Rationale:
The risk of QT prolongation may be increased in patients concomitantly treated with certain antihistamines, anti-arrhythmics, erythromycin and tricyclic antidepressants. In these cases acquired prolonged QT can precipitate fatal or life threatening arrhythmic adverse events, including torsade de pointes (TdP) but fortunately, this is only a theoretical risk. Based on this information "QT prolongation" has been classified as Important Identified Risk and cases that report torsade de pointes are included in this analysis.

Patients who had hypersensitivity to ranolazine

Reason for exclusion:
This is a standard exclusion criterion for clinical studies.

Is it considered to be included as missing information? No

Rationale:
Ranolazine is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
However, cases of angioedema showing a positive dechallenge have been observed at a high ranolazine dose (1000 mg bid), in particular in patients taking concomitant cardiovascular cosuspect drugs such as ACE inhibitors or having a previous experience of angioedema associated with ACE inhibitor treatment.

SIV.2 **Limitations to detect adverse reactions in clinical trial development programmes**

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table S IV–1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment*	Patient exposure: 28
• Patients with renal impairment**	Patient exposure: 204
• Patients with cardiovascular impairment***	Patient exposure: 3,139
• Immuno-compromised patients****	Ranolazine was administered in 14 patients who have completed standard dose chemotherapy.
• Patients with a disease severity different from inclusion criteria in clinical trials.	Not included in the clinical development program.
Population with relevant different ethnic origin	159 black patients, 156 asian patients, 1 american indian or Alaska native patient, 3 native hawaiian or other pacific islander patients, 4 hispanic patients and 45 with other ethnicities were included during the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

* Data reported from GS-US-259-0133.

** Data reported from MEIN/10/Ran-PCI/005, MEIN/10/Ran-Did/001, GS-US-259-0112, GS-US-259-0116, GS-US-259-0133.

*** Data reported from MEIN/10/Ran-PCI/005, MEIN/10/Ran-Did/001, MEIN/10/Ran-Cad/003, MEIN/11/RAN-HCM/001, RAF-01, GS-US-259-0112, GS-US-259-0113, GS-US-259-0116, GS-US-259-0133, GS-US-259-0143, GS-US-259-0131, GS-US-259-0147, CVT 3041, GS-US-259-0107, GS-US-270-0101.

**** Data reported from MEIN/09/Ran-Car/01 study.

PART II: MODULE SV. - **POST-AUTHORISATION EXPERIENCE**

SV.1 **Post-authorisation exposure**

SV.1.1 Method used to calculate exposure

In the US, ranolazine is sold as twice daily (BID) 500 and 1000 mg tablets in bottles of 60 tablets. One bottle is equivalent to a 1 month supply for 1 patient at the starting dose of 500 mg BID or the recommended daily dose of 1000 mg BID. Every 60 tablets are therefore assumed to be a 1-month supply at the labeled dose of 500 mg BID or 1000 mg BID. The assumption is made that 60 tablets last 1 month and therefore equal 1 patient-month. Therefore, it is assumed that the drug is used in the same way regardless of the prescription type or sales channel (retail, mail order, long-term care, or other channels). Physician samples are excluded from this calculation.
In the EU and other countries, ranolazine is supplied in cartons containing 30, 60, or 100 tablets in blister strips or 60 tablets in plastic bottles. Patient exposure data from the EU and other countries have been estimated based on sales figures, by assuming that 60 tablets (of 375, 500, or 750 mg tablets) represent the exposure of 1 patient for 1 month.

SV.1.2 Exposure

Cumulative worldwide patient exposure to ranolazine since first marketing approval in the US on 27 January 2006 to 31 January 2018 is estimated to be 33,878,418 patient-months. Table V-1 provides the estimated patient exposure up to 31-Jan-2018 for each country.

United States

Estimated patient-months for the US is calculated using data from the Symphony Health Pharmaceutical Audit Suite (PHAST).

Symphony Health PHAST provides prescription data for ranolazine which includes the total number of tablets issued for ranolazine prescriptions.

Cumulative patient exposure to marketed ranolazine since first marketing approval in the US on 27 January 2006 to 31 January 2018 is estimated to be 18,608,940 patient-months.

European Union and Other Countries

Cumulative exposure to marketed ranolazine in the EU and other countries (excluding the US) through 31 December 2017 is estimated to be 15,269,477 patient-months.

Table S V-1Estimated Patient Exposure to Marketed Ranolazine up to 31 January 2018

Geographic Area[a]	**Patient Exposure up to 31 January 2018**[b] **(patient-months, rounded to nearest whole number)**
USA	**18,608,940**
European Union (EU)	
Austria	206,361
Bulgaria	328
Croatia	21,601
Cyprus	5,663
Estonia	2,840
Germany	4,331,950
Greece	898,180
Ireland	306,424
Italy	4,740,604
Latvia	52,778
Lithuania	75,589
Malta	1,608
Poland	2,034
Portugal	47,719
Slovenia	132,674
Spain	2,364,766
United Kingdom	943,503
Rest of World	
Albania	39,039
Arab Emirates	4,319
Armenia	164
Azerbaijan	936
Belarus	28
Belize	60
Bosnia-Herzegovina	3,727
Costa Rica	7,888
El Salvador	6,413
Georgia	2,754
Guatemala	32,181
Honduras	5,849

Geographic Area[a]	**Patient Exposure up to 31 January 2018**[b] **(patient-months, rounded to nearest whole number)**
Hong Kong	1,785
Jordan	1,000
Kazakhstan	1,420
Kosovo	9
Kyrgyzstan	195
Lebanon	3,200
Macedonia	2
Malaysia	5,409
Moldova	320
Montenegro	174
Nicaragua	12,162
Panama	5,228
Philippines	62,008
Russia	153,808
Serbia	5,086
Singapore	4,267
Switzerland	79,031
Thailand	3,441
Turkey	680,135
Turkmenistan	1,474
Ukraine	10,782
Uzbekistan	564
Total	**33,878,418**[c]

a Territories for which no post-marketing exposure has been recorded are not included in this table.
b Cumulative patient exposure data for EU and ROW (Menarini territories) were available through 31 December 2017.
c Totals do not match figures in columns due to the effects of rounding of the values of each Geographic Area.

PART II: MODULE SVI. - **ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION**

Potential for misuse for illegal purposes

It is not believed the product could be misused for an illegal purpose.

PART II: MODULE SVII. - **IDENTIFIED AND POTENTIAL RISKS**

SVII.1 **Identification of safety concerns in the initial RMP submission**

Ranolazine is a product registered through a centralised procedure for which the European Marketing Authorisations of ranolazine were transferred from CV Therapeutics Europe Limited to Menarini International Operations Luxembourg S.A. (MIOL) on 25-Feb-2009. The first RMP for ranolazine submitted to EMA with the initial marketing authorization was the version 5.0 dated on 18-Apr-2008 with DLP 26-Jul-2007 (Registration procedure number EMEA/H/C/000805/0000) and was elaborated by CV Therapeutics Europe Limited.
The first version of the RMP that reported Menarini International Operations Luxembourg S.A. as Marketing Authorization Holder, was the version 6.0, dated 7 May 2009 with DLP 26-Jul-2007 and formally approved in August 2009. It was in effect soon after the marketing authorization was transferred from CVT Europe to Menarini.
No changes of the safety concerns were included in the version 6.0 compared to the version 5.0.
The following table reports the important safety concerns considered at the time of the first approved RMP:

Important Identified Risks	Constipation, nausea, vomiting
	Dizziness, Syncope
	Confusion
	Hypotension
	QT prolongation
Important Missing Information	Effects on male infertility
	Use in pregnant or lactating women and the pediatric population
	Ethnicity other than Caucasian
	Safety information for patients with moderate and severe hepatic impairment
	Safety information for patients with severe and end-stage renal disease requiring dialysis
	Drug-drug interactions with Class Ia and Class III antiarrhythmics except amiodarone
	Antihistamines (eg, terfenadine, astemizole, mizolastine), certain antiarrhythmics (eg, quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (eg, imipramine, doxepin, amitriptyline)
	Real-world safety information for drug-drug interactions with potent CYP3A4 inhibitors which may cause ranolazine plasma concentration increases
	Drug-drug interactions with CYP2D6 substrates (eg, tricyclic antidepressants and antipsychotics)

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The majority of the risks not considered important and not included in the safety concerns list were those not associated to a relevant risk or they were associated with a low frequency during the clinical development.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Renal and urinary disorders: dysuria, haematuria, chromaturia, acute renal failure, urinary Retention;
- Hepatic disorders: elevated levels of hepatic enzyme;
- Metabolism and nutrition disorders: dehydration;
- Eye disorders: blurred vision, visual disturbance, diplopia;
- Respiratory system disorders: dyspnoea, cough, epistaxis and throat tightness;
- Reproductive system and breast disorders: erectile dysfunction;
- General disorders and administration site conditions: asthenia, fatigue, peripheral oedema;
- Investigations: increased blood creatinine, increased blood urea, increased platelet or white blood cell count, decreased weight;
- Musculoskeletal and connective tissue disorders: pain in extremity, muscle cramp, joint swelling;
- Ear and labyrinth disorders: tinnitus, vertigo, impaired hearing.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. action being part of standard clinical practice in each EU Member state where the product is authorized):

- None

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

Anorexia, decreased appetite, pruritus, hyperhydrosis, allergic dermatitis, urticaria, cold sweat and rash are uncommon adverse reactions with minimal impact on patients.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: QT prolongation

Risk-benefit impact:
Data collected in placebo-treated patients enrolled in CVT 3036 study provide a valuable source for providing a background incidence of cardiac AESI that could be triggered by QT prolongation. In particular, continuous 7-day Holter monitoring revealed that the incidence of clinically significant arrhythmias was significantly reduced by ranolazine. The results from CVT 3036, together with findings from nonclinical studies, indicate that ranolazine does not have proarrhythmic potential and in fact has antiarrhythmic properties.
The risk of QT prolongation may be increased in patients concomitantly treated with certain antihistamines, anti-arrhythmics, erythromycin and tricyclic antidepressants. In these cases acquired prolonged QT can precipitate fatal or life threatening arrhythmic adverse events, including torsade de pointes (TdP) but luckily, this is only a theoretical risk. Based on this information, QT prolongation has been considered an Important Identified Risk.

Important Potential Risk: Myasthenic syndrome

Risk-benefit impact:
The mechanism through which ranolazine would precipitate myasthenic syndrome or myasthenia gravis is unknown. Myasthenia gravis is an autoimmune neuromuscular disease characterized by anti-acetylcholine receptor (AChR) antibodies which mount an immune-mediated attack on postsynaptic neuromuscular junctions. Very few suspected cases of myasthenic syndrome have been collected in the clinical and post-marketing experience with ranolazine but considering that the myasthenic syndrome is a serious event that has a major impact on the patient's life, this issue has been considered an Important Potential Risk.

Important Potential Risk: Cardiac arrhythmias

Risk-benefit impact:
According to the PRAC Rapporteur's preliminary assessment report (Procedure n.EMEA/H/C/PSUSA/00002611/201801), "Cardiac arrhythmias was suggested to be added as important potential risk in the RMP.

The signal of "Cardiac arrhythmias" was initiated by FDA due to findings in the Adverse Event Reporting System for period Q1 2016. However, the type and frequency of "Cardiac arrhythmias" reported as treatment emergent adverse events (AEs) from two large multicenter international studies (CVT 3036 [MERLIN-TIMI] and GS-US-259-0116 [RIVER-PCI]) were comparable between placebo and ranolazine treatment groups.

Results of 7-day continues ECG (Holter) monitoring in Study CVT 3036 also demonstrated that, compared to placebo treated subjects, ranolazine-treated patients had fewer episodes of clinically significant arrhythmias. Additionally, significantly fewer ranolazine-treated patients experienced an episode of ventricular tachycardia lasting $\geqslant$ 8 beats compared to placebo patients.
These clinical data indicate that ranolazine does not have proarrhythmic potential.

This signal was closed by MAH, which was agreed by the Rappoteur who however proposed that "Cardiac arrhythmias" should be included as important potential risk in the RMP due to the fact that in both MERLIN-TIMI and RIVER-PCI studies the PT "cardiac arrest" and only in MERLIN-TIMI, the PTs "bradycardia" and "supraventricular tachycardia" were reported with numerically higher incidence in ranolazine group compared to placebo:
Cardiac arrest in MERLIN-TIMI [19 (<1%) vs 10(<1%)] and in RIVER-PCI [5(0.4%) vs 3 (0.2%)] respectively.
Bradycardia and supraventricular tachycardia only in MERLIN-TIMI [65(2%) vs 44(1%); 8(<1%) vs 4(<1%)] respectively.

SVII.2 **New safety concerns and reclassification with a submission of an updated RMP**

RMP v 6.1 vs v 6.0

"Drug-Drug interaction with statins which are sensitive to CYP3A4 inhibition (simvastatin, lovastatin)" was added as important identified risks.
The safety concerns were updated following the requests received during the assessment of the EU PSUR#6 with covered period from 27-Jul-2010 to 26-Jan-2011 (CHMP opinion EMA/578450/2011 issued on 19-Jul-2011).

RMP v 7.0 vs v 6.1

"Hallucination", "Angioedema", and "Drug-Drug interaction with immunosuppressants with a narrow therapeutic index metabolized by CYP3A4 (ciclosporin, tacrolimus, sirolimusm, everolimus)" were added as important identified risks.
"Drug-Drug interaction with metformin" was added among the safety concerns as important interaction (no important risk identified).

The safety concerns were updated following the requests received during the assessment of the EU PSUR#6 with covered period from 27-Jul-2010 to 26-Jan-2011 (CHMP opinion EMA/578450/2011 issued on 19-Jul-2011) and following the variation EMEA/H/C/000805/II/030, in order to include newly identified safety issue in the post-marketing experience.

RMP v 7.1 vs v 7.0

"Drug-Drug interaction with metformin" previously erroneously identified as "important interaction" was reclassified as important potential risk.

This formal correction was performed following the requests received during the assessment of the EU PSUR#7 with covered period from 27-Jan-2011 to 26-Jan-2012 (CHMP opinion EMA/438953/2012 issued on 05-Jul-2012).

RMP v 7.2 vs v 7.1

No change concerning the identified/potential risk or missing information.

RMP v 8.0 vs v 7.2

"Constipation, nausea and vomiting" previously classified as important identified risk is removed from the list of safety concerns.
"Confusion, Hallucination" previously classified as important identified risk is removed from the list of safety concerns.
"Drug-Drug interaction with immunosuppressants with a narrow therapeutic index metabolized by CYP3A4 (ciclosporin, tacrolimus, sirolimus, everolimus)" previously classified as important identified risk is removed from the list of safety concerns.
Given the cumulative experience, the relatively benign medical implication and results from the IMS Disease Analyser study (MEN-RAN-303-IMS.001), in connection with the PSUR assessment of the EU PSUR# 8 (EMA/PRAC/493878/2013 concerning the Procedure No.: EMEA/H/C/805/PSU 018), the PRAC rapporteur accepted the deletion of these important safety concerns (PRAC assessment EMA/PRAC/543523/2013 for the European Risk Management Plan (EU-RMP) Version 7.2).
The IMS Disease Analyser study was proposed at the time of product registration in Europe via centralized procedure and it was included in the ranolazine EU-RMP as an additional pharmacovigilance activity for most of the identified safety concerns. The final results from IMS Disease Analyser study were presented in the Annex 4 of RMP version 7.2 , therefore, this study is no longer considered an additional pharmacovigilance activity in the currently RMP.

"Myasthenic syndrome" is a new important potential risk.
The addition of Myasthenic syndrome to the list of safety concerns has been performed according to the PRAC assessment of the EU PSUR#8 (EMA/PRAC/493878/2013 concerning the Procedure No.: EMEA/H/C/805/PSU 018).

The important potential risk "Drug-Drug interaction with metformin" has been renamed in "Drug-Drug PK interaction with metformin".

RMP v 8.1 vs v 8.0

The following changes of safety concerns have been performed according to the PRAC Rapporteur's preliminary assessment report, issued on 09 July 2018, in the frame of the assessment of PSUSA Procedure n. EMEA/H/C/PSUSA/00002611/201801 of the EU PSUR#10 with covered period 27 January 2015_ 26 January 2018.

"Dizziness, syncope", "Hypotension", "QT prolongation", "Angioedema" and "Drug-drug interaction with statins which are sensitive to CYP3A4 inhibition (simvastatin, lovastatin)" previously classified as important identified risks are removed from the list of safety concerns.

"Drug-Drug PK Interaction with metformin" previously classified as important potential risk is removed from the list of safety concerns because it is sufficiently described in the section 4.5 of the SmPC.

"Cardiac arrhythmias" is a new important potential risk. The Rappoteur proposed that this risk should be included as important potential risk in the RMP due to the fact that in both MERLIN-TIMI and RIVER-PCI studies the PT "cardiac arrest" and only in MERLIN-TIMI,

the PTs "bradycardia" and "supraventricular tachycardia" were reported with numerically higher incidence in ranolazine group compared to placebo.

"Effect on male fertility", "Use in pregnant or lactating women and the paediatric population", and "Ethnicity other than Caucasian" previously classified as missing information are removed from the list of safety concerns. There are no ongoing pharmacovigilance activities and there is no reasonable expectation that future pharmacovigilance activities could further characterise the safety profile of ranolazine.

"Safety information for patients with moderate and severe hepatic impairment ", "Safety information for patients with severe and end stage renal disease requiring dialysis", "Real-world safety information for drug-drug interactions with potent CYP3A4 inhibitors which may cause ranolazine plasma concentration increases" and "Drug-drug interaction with Class Ia and Class III antiarrhythmics except amiodarone" previously classified as missing information are removed from the list of safety concerns. Ranolazine is contraindicated in moderate or severe hepatic impairment, severe renal impairment, with concomitant use with potent CYP3A4 inhibitors and with Class Ia or Class III antiarrhythmics other than amiodarone. Therefore, it is not expected that the product will be used in these populations/situations.

"Drug-drug interactions with CYP2D6 substrates (eg, tricyclic antidepressants and antipsychotics)" previously classified as missing information is removed from the list of safety concerns. This interaction is sufficiently described in the SmPC.

"Antihistamines (eg, terfenadine, astemizole, mizolastine), certain antiarrhythmics (eg, quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (eg, imipramine, doxepin, amitriptyline)" previously classified as missing information is removed from the list of safety concerns. The concomitant treatment of ranolazine with other drugs known to prolong the QTc interval is described in the SmPC.

RMP v 8.2 (current) vs v 8.1

The following change of safety concerns has been performed according to the PRAC Rapporteur's updated assessment report, issued on 22 August 2018, in the frame of the assessment of PSUSA Procedure n.EMEA/H/C/PSUSA/00002611/201801 of the EU PSUR#10 with covered period 27 January 2015_ 26 January 2018.

"QT prolungation" has been restored as an important identified risk.

SVII.3 **Details of important identified risks, important potential risks, and missing information**

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: QT prolongation

Potential mechanisms:
The effects of ranolazine on the surface electrocardiogram (prolongation of QTc interval) are believed to result from inhibition of the fast-rectifying potassium current, which prolongs the ventricular action potential; inhibition of the late sodium current by ranolazine shortens the ventricular action potential. In CVT 3114, administration of ranolazine resulted in a mean reduction in QTc interval of −26.3 ± 3.49 msec ($p < 0.001$) for patients with LQT3 due to mutation in the SCN5A sodium-channel gene. Shortening the QTc interval in patients with LQT3 syndrome, without affecting ventricular conduction, supports the nonclinical and clinical body of evidence for the lack of proarrhythmic potential of ranolazine.

Evidence source(s) and strength of evidence:
Data collected in placebo-treated patients enrolled in CVT 3036 study provide a valuable source for providing a background incidence of cardiac AESI that could be triggered by QT prolongation. In particular, continuous 7-day Holter monitoring revealed that the incidence of clinically significant arrhythmias was significantly reduced by ranolazine, as shown in the below table.

	Placebo (n = 3273)	Ranolazine (n = 3268)
Number of patients with Holter data	3189	3162
Incidence of clinically relevant arrhythmias	2650 (83.1%)	2330* (73.7%)
Any VT ≥ 100 bpm ≥ 3 beats	1211 (38.0%)	948 (30.0%)
Any SVT ≥ 120 bpm	1752 (54.9%)	1413 (44.7%)
New onset AF	75 (2.4%)	55 (1.7%)
Any bradycardia	1485 (46.6%)	1257 (39.8%)

Extracted from CVT 3036 Clinical Study Report, Table 24; * $p<0.001$ vs. placebo. VT =Ventricular tachycardia, SVT Sustained Ventricular tachycardia, AF = Atrial fibrillation.

A further post-hoc evaluation of the 7-day Holter monitoring records was performed to identify ventricular tachycardias of longer duration. Analysis of these data showed that ranolazine significantly decreased the incidence of ventricular tachycardia (VT) ≥ 8 beats, and had no adverse effect on sustained or polymorphic VT as shown in the below table.

	Placebo n (%)	Ranolazine n (%)
Number of patients with Holter data	3189	3162
VT ≥ 8 beats	265 (8.3%)	166* (5.2%)
Polymorphic VT (≥ 8 beats)	46 (1.4%)	38 (1.2%)
Sustained VT (>30 sec)	14 (0.4%)	14 (0.4%)
Monomorphic	7 (0.2%)	4 (0.1%)
Polymorphic	7 (0.2%)	10 (0.3%)

Source: D120 Responses, Summary of Clinical Safety Table 2.7.4:8; * p<0.001 vs placebo.

The reduction in VT ≥ 8 beats was consistently observed among several high-risk subgroups, including patients with prior CHF, low ejection fraction (EF ≤ 40%), high TIMI risk score (5–7), and prolonged QT interval at baseline (≥ 450 msec, see Table below).

Number of patients with prolonged QT interval at baseline ≥ 450 msec	Placebo n (%) 600	Ranolazine n (%) 591
VT ≥ 8 beats	63 (10.5%)	33* (5.6%)

Source: D120 Responses, Question 24, Table 24:7; * p<0.002 vs. placebo.

There was no difference in rate of sudden deaths reported throughout the duration of the study among these high-risk subgroups (Karwatowska-Prokopczuk 2013), as displayed in the below table.

	Placebo	Ranolazine
Number of sudden cardiac deaths	22	15
Relative risk ranolazine vs. placebo (95% CI)	039 (0.36-1.33) p = 0.26	

Source: D120 Responses, Question 24, Table 24:7.

In MEN-RAN-303-IMS.001 study QT Prolongation was a historical diagnosis for 0.11% and 0.13% of patients to whom ranolazine or other antiangina drugs will be prescribed, respectively.

A recent study has determined the prevalence of atrial fibrillation and mortality in the general population and in patients with CV diseases. The groups included 3960 individuals randomly selected from the population, aged 45+; 782 patients with a previous diagnosis of heart failure; and 1062 patients with a record of myocardial infarction, hypertension, angina, or diabetes. In the general population the prevalence of atrial fibrillation was 2% (1.6% in women and 2.4% in men), rising with age from 0.2% in those 45–54 years of age to 8.0% in those 75 years and older. This rose to 5.7% in patients with myocardial infarction, 4.7% in those with angina, and 5.3% in diabetics and 22% in patients with heart failure. Adjusting for age and sex, mortality was 1.57 times higher in patients with atrial fibrillation.

On the other hand, the prevalence of ventricular fibrillation/tachycardia was 6.2% amongst 59,161 patients enrolled in the Global Registry of Acute Coronary Events Study between

2000 and 2007 and hospital death rates were 55.3% and 1.5% in patients with and without ventricular fibrillation/tachycardia, respectively (McManus 2012).
Therefore, based on the published literature, a background of major cardiac events such as Torsade de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac death is expected in the general population, with an obvious increase in the prevalence of these events in patients with history of cardiovascular diseases, regardless of ranolazine treatment. Rather, ranolazine has shown a protective effect on some of these events.
Based on these information, QT prolongation has been classified as Important Identified Risk.

Characterisation of the risk:

Clinical studies

The QT prolongation by ranolazine is well characterised and is dose dependent. The below table displays the QT interval by dose in Phase 2/3 studies for angina.

Number of patients	QT interval: difference from baseline (msec) and SD					
	Placebo	500 BID	750 BID	1000 BID	1500 BID	total
	439	177	269	434	173	706
QT interval	−3.1 ± 21.0	1.3 ± 23.1	7.0 ± 23.7	6.6 ± 22.2	10.5 ± 24.9	6.7 ± 22.3
QTcB interval	−2.0 ± 19.1	2.1 ± 24.7	3.7 ± 13.6	4.6 ± 17.2	8.7 ± 25.9	4.6 ± 15.7
QTcF interval	−2.3 ± 15.6	1.9 ± 20.6	4.9 ± 12.6	5.4 ± 14.7	9.5 ± 22.3	5.4 ± 13.7

Mean changes were calculated over the duration of treatment and were not correlated with peak/trough measurements. QTcB = Bazett's correction. QTcF = Fridericia correction.

A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000 mg BID.
This value is highly consistent with data from pivotal clinical studies, where, at the time of approximate peak plasma concentration after doses of 500 to 1000 mg twice daily, QTcF (Frederica's correction) changed from baseline up to a mean of 6.6 msec. Age, weight, gender, race, diabetes, presence or absence of heart failure, baseline heart rate, baseline QTc, dose (single and total daily dose), patient status (healthy volunteer/patient), ranolazine formulation, and study did not affect the slope of the relationship in the population PK model. The slope is higher in patients with clinically significant hepatic impairment.
An estimate of the incidences and 95% CI of QT/QTc prolongation in CVT 3036 study is provided in the below table.

Treatment	QT prolonged	QTc prolonged
Placebo	0.1% (0.0%-0.2%)	0.3% (0.1%-0.5%)
Ranolazine	0.4% (0.2%-0.7%)	0.5% (0.3%-0.8%)

Safety information on the clinical outcomes of QT prolongation was specifically studied in CVT 3036, in which patients who were receiving standard of care therapy for acute coronary

syndrome (54% with chronic angina) were treated with ranolazine at a dose of 1000 mg bid and followed for an average of ~1 year. There was no difference between ranolazine and placebo groups in the risk of all-cause mortality (relative risk ranolazine: placebo 0.99), sudden cardiac death (relative risk ranolazine:placebo 0.87), or the frequency of symptomatic documented arrhythmias (3.0% versus 3.1%) in the 6560 patients with UA/NSTEMI ACS (CVT 3036). No proarrhythmic effects were observed in the 3162 patients treated with ranolazine based on 7-day Holter monitoring in CVT 3036. There was a significantly lower incidence of arrhythmias in patients treated with ranolazine (74%) versus placebo (83%); including ventricular tachycardia ≥ 8 beats (5% versus 8%). The effect was also observed in subgroups of patients at high risk for developing arrhythmias (ie, baseline QTc ≥ 450 msec), where ranolazine significantly decreased the frequency of ventricular tachycardia lasting greater than 8 beats. In addition, these subgroups did not show increased risk of sudden death upon treatment with ranolazine. In CVT 3036, the rate of discontinuations due to QT prolongation was low: 2 (< 1%) placebo patients and 9 (< 1%) ranolazine patients.

There is no evidence that prolongation of the QTc interval associated with ranolazine results in any increased risk of ventricular arrhythmias or mortality in high risk patients, including those with prolonged QTc values (≥ 450 msec). The results from CVT 3036, together with findings from nonclinical studies, demonstrate that concentrations of ranolazine that prolong the QTc interval do not provoke conditions which underlay the pathophysiological mechanisms for the initiation and maintenance of TdP, such as early after depolarizations, triggered activity, ventricular tachycardia, or an increase in the spatial dispersion of the duration of ventricular repolarization, and indicate that ranolazine does not have proarrhythmic potential and in fact has antiarrhythmic properties.

Post-marketing
A search was carried out in the Company Global Safety Database using the following MedDRA (v. 20.1) PTs: "Cardiac death", "QT interval prolonged", "Sudden death", "Torsade de pointes", "Ventricular fibrillation" and "Ventricular tachycardia".

Up to the DLP (26-Jan-2018) a total of 69 ADRs (67 of which serious and 2 non serious) were reported in 58 ICSRs (56 of which serious) from spontaneous and literature post-marketing sources.

The reported PTs with this search strategy were: "Cardiac death" (n = 1, serious), "Sudden death" (n = 11, all serious), "Torsade de pointes" (n = 28, all serious), "Ventricular fibrillation" (n = 7, all serious) and "Ventricular tachycardia" (n = 22, 20 of which serious).

In addition, 9 serious ADRs were reported in 8 ICSRs from non-interventional post-marketing study and other solicited sources. The reported PTs were: "Ventricular fibrillation" (n = 3) and "Ventricular tachycardia" (n = 6).

Cumulatively, 78 ADRs (76 of which serious) in 66 ICSRs (64 of which serious) were identified.

The outcome of ADRs was: fatal (n = 16), resolved (n = 34), resolved with sequelae (n = 1), continuing (n = 2), not reported (n = 17) and unknown (n = 8).

Up to the DLP of this report (26-Jan-2018), the reporting rate (rr) of this risk was 1.95 ICSRs per million patient/month (66 ICSRs/33.88 million patient/month), considering all sources identified during the post-marketing experience.

Risk factors and risk groups:
Risk factors for QTc prolongation include populations not evaluated in the clinical program:
• Concomitant administration of drugs that prolong the QT interval;
• Patients with a history of congenital or a family history of long QT syndrome other than LQT3.
In patients with a combination of these factors, along with others such as electrolyte disturbances, female gender, family history of ventricular arrhythmias or early sudden cardiac death, risk of serious events may be increased.
In MEN-RAN-303-IMS.001 study the only patient with QT prolongation in the ranolazine group was older than 65 years. In the control group 67% of patients with ventricular arrhythmia were older than 65 years. The only patient with QT prolongation in the ranolazine group had a co-prescription of moderate or weak CYP3A4 inhibitors, whereas 5.3% of patients experiencing QT prolongation in the control group were treated with these drugs. ACE inhibitors and CYP2D6 substrates were the most common drugs taken by patients receiving other antiangina drugs and experiencing ventricular arrhythmia; however as ACE inhibitors and CYP2D6 substrates (eg, most beta-blockers) are prescribed for cardiovascular diseases, it seems obvious that they represent the treatment of the disease, rather than risk factors.

Preventability:
The use of ranolazine in patients with severe hepatic impairment or with concomitant strong CYP3A4 inhibitors is contraindicated in the common EU SmPC. It includes also cautions for use of ranolazine when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval. There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Drugs that may be of concern when used with ranolazine are for example certain antihistamines (eg, terfenadine, astemizole, mizolastine), certain antiarrhythmics (eg, quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (eg, imipramine, doxepin, amitriptyline). Physicians who prescribe ranolazine should counsel their patients concerning the nature and implications of underlying diseases and disorders that are considered risk factors, demonstrated and predicted drug-drug interactions, and symptoms suggestive of arrhythmia.
The current EU SmPC address this risk at section 4.4 “Special warnings and precautions for use” and 5.2 “Pharmacokinetic properties”.

Additionally, a specific form has been developed to follow-up cases which may involve QT/QTc interval prolonged, ventricular tachycardia, ventricular fibrillation, and Torsade de pointes.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate (rr) of 1.95 ICSRs of QT prolongation per million patient/month (66 ICSRs/33.88 million patient/month), considering all sources identified during the post-marketing experience.
Due to the low incidence, additional risk minimisation measures are not considered necessary, and those already implemented are sufficient.

Public health impact:
Acquired prolonged QT caused by certain drugs can precipitate fatal or life-threatening arrhythmic adverse events, including torsade de pointes (TdP). There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.

Important Potential Risk: Myasthenic syndrome

Potential mechanisms:
The mechanism through which ranolazine would precipitate myasthenic syndrome or myasthenia gravis is unknown.
Myasthenia gravis is an autoimmune neuromuscular disease characterized by anti-acetylcholine receptor (AChR) antibodies which mount an immune-mediated attack on postsynaptic neuromuscular junctions. AChR antibodies are measurable in 85% of all patients.
Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic disorder in which auto-antibodies affect pre-synaptic neuromuscular junctions, resulting in decreased acetylcholine release from nerve terminals.
Three clinical scenarios have been described in the literature with respect to medications and their role in myasthenic syndromes:

- Patients with known myasthenia gravis or LEMS may have worsening of symptoms on exposure to some antiinfectives (eg, aminoglycosides), cardiovascular drugs (eg, beta-blockers, procainamide), and anti-epileptics or anesthetic neuromuscular blocking agents (eg, phenytoin);
- Patients with asymptomatic or previously unrecognized/subclinical myasthenia gravis may experience 'unmasking' of the underlying condition when exposed to antiarrhythmic medications such as quinidine and quinine;
- Patients with no known history of myasthenia gravis develop an AChR antibody positive iatrogenic myasthenic syndrome during treatment with d-penicillamine (up to 7%). The syndrome usually manifests with mild ocular symptoms, and resolves on dechallenge and/or treatment with cholinesterase inhibitors. Although the exact mechanism is unclear, the observation that d-penicillamine is associated with immune-mediated complications such as systemic lupus erythematosis and polymyositis suggests that the drug-related myasthenic syndrome may be immune-mediated.

The onset of drug-related myasthenic symptoms is variable and has been noted to occur 2 to 12 months following d-penicillamine initiation and 6 to 9 months after starting interferon alpha treatment. Drug discontinuation does not always lead to immediate recovery. Symptoms typically resolve in the majority of patients within 2 to 6 months following d-penicillamine discontinuation, but have been shown to persist in 30% of patients at 1 year especially in

those with underlying autoimmune disease and subclinical myasthenia gravis. There is also at least 1 reported case of symptom persistence 7 months after interferon alpha was stopped.

Evidence source(s) and strength of evidence:
No cases of myasthenic syndrome or myasthenia gravis have been collected in patients treated with placebo during clinical trials. The incidence of events suggestive of symptoms of myasthenic syndrome (abasia, asthenopia, choking, coordination abnormal, diplopia, dysarthria, dysphagia, dysphonia, dysstasia, gait disturbance, motor dysfunction, muscle fatigue, muscular weakness, and urinary incontinence) in these patients was 0.68% (Phase 2 /3 angina studies) or 0.70% (CVT 3036 study).
Based on epidemiological population-based studies, the estimated prevalence per 100,000 of myasthenia gravis in the general population is 20 in the US and 14.6 in the UK (Phillips 2003, Robertson 1998). The prevalence of Lambert–Eaton myasthenic syndrome is 3.4 cases per million (Titulaer 2011).
Based on this information and the possible impact on the quality of life, myasthenic syndrome has been classified as Important Potential Risk.

Characterisation of the risk:

Clinical studies

No cases reporting myasthenia gravis or myasthenic syndrome have been collected in angina studies. In Phase 2/3 studies for angina, events suggestive of symptoms of myasthenic syndrome have been reported in both ranolazine and placebo-treated patients.

Phase 2/3 PR Controlled Angina Studies		
	Placebo (n = 738)	**Ranolazine (n = 1,030)**
Number of events	5	17
Frequency with 95% CI	0.68% (0.22-1.57)	1.65% (0.96-2.63)

In the CVT 3036 study, 1 event of myasthenia gravis has been collected in patients treated with ranolazine out of 3268 (incidence 0.03%, 95% CI 0.00-0.17). In the CVT 3036 study, events suggestive of symptoms of myasthenic syndrome have been reported in both ranolazine and placebo-treated patients.

CVT 3036 Study		
	Placebo (n = 3273)	**Ranolazine (n = 3268)**
Number of events	23	38
Frequency with 95% CI	0.70% (0.45-1.05)	1.16% (0.82-1.59)

In phase 2/3 studies for angina, events suggestive of symptoms of myasthenic syndrome did not meet the seriousness criteria. The event of myasthenia gravis collected in CVT 3036 study did not meet the seriousness criteria. In CVT 3036 study, one event suggestive of symptoms of myasthenic syndrome (diplopia) met the seriousness criteria.

In Phase 2/3 studies for angina, the following events suggestive of symptoms of myasthenic syndrome were collected.

Phase 2/3 PR Controlled Angina Studies		
	Placebo (n = 738)	**Ranolazine (n = 1,030)**
Myasthenia (eg, muscular weakness)	3 (0.41%)	8 (0.78%)
Dysphagia	0	4 (0.39%)
Abnormal gait (eg, Gait disturbance)	1 (0.14%)	3 (0.29%)
Urinary incontinence	0	2 (0.19%)
Incoordination (Coordination abnormal)	1 (0.14%)	0

In the CVT 3036 study, the following events suggestive of symptoms of myasthenic syndrome were collected.

CVT 3036 Study		
	Placebo (n = 3273)	**Ranolazine (n = 3268)**
Diplopia	4 (0.12%)	10 (0.31%)
Dysphagia	3 (0.09%)	8 (0.24%)
Urinary incontinence	3 (0.09%)	5 (0.15%)
Muscle fatigue	4 (0.12%)	5 (0.15%)
Dysphonia	4 (0.12%)	4 (0.12%)
Dysarthria	1 (0.03%)	3 (0.09%)
Myasthenia gravis	0	1 (0.03%)
Coordination abnormal	0	1 (0.03%)
Muscular weakness	3 (0.09%)	1 (0.03%)
Incontinence	1 (0.03%)	0

It should be observed that, in both angina and the CVT 3036 studies, events concerning the skeletal muscle function (eg, Muscle fatigue, Muscular weakness) occurred in both placebo, and ranolazine-treated patients with an incidence that was not much different between the 2 groups, indicating that these symptoms are found in these populations regardless of ranolazine treatment.

Post-marketing
A search was carried out in the Company Global Safety Database using the following MedDRA (v. 20.1) PTs: “Myasthenia gravis” or “Myasthenic syndrome” or cases that contained at least 2 of the following PTs: “Abasia”, “Asthenopia”, “Choking”, “Coordination abnormal”, “Diplopia”, “Dysarthria”, “Dysphagia”, “Dysphonia”, “Dysstasia”, “Gait disturbance”, “Motor dysfunction”, “Muscle fatigue”, “Muscular weakness” and “Urinary incontinence”.

Up to the DLP (26-Jan-2018) a total of 25 ADRs (11 of which serious and 14 non serious) were reported in 13 ICSRs (11 of which serious) from spontaneous and literature post-marketing sources.

The reported PTs with this search strategy were: "Myasthenia gravis" (n = 2, all serious), "Coordination abnormal" (n = 1, non serious), "Diplopia" (n = 1, serious), "Dysarthria" (n = 2, all non serious), "Dysphagia" (n = 3, 1 of which serious), "Dysstasia" (n = 1, serious), "Gait disturbance" (n = 5, 1 of which serious), "Motor dysfunction" (n = 2, all serious), "Muscle fatigue" (n = 1, non serious), "Muscular weakness" (n = 6, 2 of which serious) and "Urinary incontinence" (n = 1, serious).

In addition, 7 serious ADRs were reported in 4 ICSRs from non-interventional post-marketing study and other solicited sources. The reported PTs were: "Myasthenia gravis" (n = 1), "Choking" (n = 1), "Dysphagia" (n = 1), "Dysphonia" (n = 1), "Gait disturbance" (n = 2) and "Motor dysfunction" (n = 1).

Cumulatively, 32 ADRs (18 of which serious) in 17 ICSRs (15 of which serious) were identified.

The outcome of ADRs was: resolved (n = 4), resolving (n = 2), continuing (n = 4), not reported (n = 20) and unknown (n = 2).

Up to the DLP of this report (26-Jan-2018), the reporting rate (rr) of this risk was 0.50 ICSRs per million patient/month (17 ICSRs/33.88 million patient/month), considering all sources identified during the post-marketing experience.

Risk factors and risk groups:
Women are twice as likely as men to be affected by myasthenia gravis. Onset of this disease can occur at any age; however, women under the age of 40 years and men over the age of 60 years are most commonly affected (Robertson 1998). Around 60% of those with Lambert–Eaton myasthenic syndrome have an underlying malignancy.
Too few suspected cases describing relevant AESI have been collected in clinical studies and post-marketing surveillance for the identification of risk factors in patients which could potentially develop myasthenic syndrome following ranolazine.

Preventability:
In the absence of the identification of risk factors, it will not be possible to prevent the occurrence of myasthenic syndrome potentially triggered by ranolazine.
However, the current EU SmPC address this risk at section 4.8 "Undesirable effects".

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate (rr) of 0.50 ICSRs of myasthenic syndrome per million patient/month (17 ICSRs/33.88 million patient/month), considering all sources identified during the post-marketing experience.
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
Very few suspected cases of myasthenic syndrome have been collected in the clinical and post-marketing experience with ranolazine, therefore an eventual causal relationship between this drug and myasthenic syndrome would have a minimal public health impact.

Important Potential Risk: Cardiac arrhythmias

Potential mechanisms:
According to the PRAC Rapporteur's Preliminary Assessment Report (Procedure no.: EMEA/H/C/PSUSA/00002611/201801), "Cardiac arrhythmias" was added as important potential risk.

The signal of "Cardiac arrhythmias" was initiated by FDA due to findings in the Adverse Event Reporting System for period Q1 2016. However, the type and frequency of "Cardiac arrhythmias" reported as treatment emergent adverse events (AEs) from two large multicenter international studies (CVT 3036 [MERLIN-TIMI] and GS-US-259-0116[RIVER-PCI]) were comparable between placebo and ranolazine treatment groups.

There are two potential drug interaction mechanisms that have the potential to increase arrhythmic risk. As ranolazine prolongs the QTc interval in a dose-related manner, one mechanism is the pharmacodynamic interaction which is an additive effect with concurrent administration of two or more agents that prolong the QT interval through interactions via potassium channels. The other mechanism is pharmacokinetic where an interacting drug increases serum concentrations of ranolazine as a result of reduced drug clearance (Liu BA. et al, 2004).

Many of the major pharmacokinetic interactions between drugs are due to hepatic cytochrome P450 (P450 or CYP) enzymes being affected by administration of other drugs. Ranolazine is a substrate of cytochrome CYP 3A4, and therefore serum concentrations of ranolazine can be increased when administered with a drug that strongly inhibits CYP 3A4 activity (Roden DM., 2004, Zhou S. et al., 2005) Consequently, ranolazine administration is contraindicated with concomitant administration of potent CYP 3A4 inhibitors (eg, itraconazole, ketoconazole, voriconazol, posaconazol, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone). Additionally, co-administration of medications that are CYP 3A4 substrates may lead to saturation of the metabolic pathway, potentially leading to decreased drug clearance and increased serum concentration of one of more of the drugs metabolized by CYP 3A4.

A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval.

Dose and plasma concentration-related increases in the QTc interval (about 6 msec at 1000 mg twice daily), reductions in T wave amplitude, and in some cases notched T waves, have been observed in patients treated with Ranexa. These effects of ranolazine on the surface electrocardiogram are believed to result from inhibition of the fast-rectifying potassium current, which prolongs the ventricular action potential, and from inhibition of the late sodium current, which shortens the ventricular action potential. A population analysis of combined data from1, 308 patients and healthy volunteers demonstrated a mean increase in QTc from baseline of 2.4 msec per 1000 ng/ml ranolazine plasma concentration. This value is consistent with data from pivotal clinical studies, where mean changes from baseline in QTcF (Fridericia' s correction) after doses of 500 and 750 mg twice daily were 1.9 and 4.9 msec, respectively. The slope is higher in patients with clinically significant hepatic impairment.

Evidence source(s) and strength of evidence:
The signal of "Cardiac arrhythmias" was initiated by FDA due to the results of disproportionality analysis (DPA) using the 2016 Q1 release of AERS+SRS, where a search of the FDA Adverse Event Reporting System (FAERS) resulted in an EB05 score > 2 for a number of terms relating to cardiac arrhythmias/conduction abnormalities.
After a review (DLP 23-Oct-2016) of cumulative postmarketing, epidemiological and clinical study data, the signal was closed by MAH, which was agreed by the the Rappoteur who however proposed that "Cardiac arrhythmias" should be included as important potential risk in the RMP due to the fact that in both MERLIN-TIMI and RIVER-PCI studies the PT "cardiac arrest" and only in MERLIN-TIMI, the PTs "bradycardia" and "supraventricular tachycardia" were reported with numerically higher incidence in ranolazine group compared to placebo:
Cardiac arrest in MERLIN-TIMI [19 (<1%) vs 10(<1%)] and in RIVER-PCI [5(0.4%) vs 3 (0.2%)] respectively.
Bradycardia and supraventricular tachycardia only in MERLIN-TIMI [65(2%) vs 44(1%); 8(<1%) vs 4(<1%)] respectively.

Characterisation of the risk:

Clinical studies
Cardiac arrhythmias reported as Treatment Emergent Adverse Events (AEs) from the following two large multi-national studies are presented in Table S VII-1:

- CVT 3036: Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN-TIMI 36);

- GS-US-2599-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Ranolazine on Major Adverse Cardiovascular Events in Subjects with a History of Chronic Angina Who Undergo Percutaneous Coronary Intervention with IncompleteRevascularization (RIVER-PCI).

The types and frequency of cardiac arrhythmias reported as treatment emergent AEs in these 2 studies are similar between placebo and ranolazine treatment groups.
Additionally, results of the 7-day continuous ECG (Holter) monitoring in Study CVT 3036 (patients with non-ST segment elevation acute coronary syndromes) demonstrated that,

compared to placebo patients, ranolazine-treated patients had fewer episodes of clinically significant arrhythmias (including ventricular tachycardia ⩾ 3 beats, supraventricular tachicardia with a ventricular rate of ⩾ 120 bpm, new onset atrial fibrillation, and bradyarrhythmia with a ventricular rate < 40 bpm or 3rd degree atrioventricular block). Further, significantly fewer ranolazine-treated patients had an episode of ventricular tachycardia lasting ⩾ 8 beats compared to placebo patients; this was also true for subgroups of patients at high risk for developing arrhythmias (eg, EF ⩽ 40%, QTc ⩾450 msec, TIMI risk score 4–7, history of heart failure), where ranolazine significantly decreased the frequency of ventricular tachycardia lasting longer than 8 beats (Table S VII-2).

Table S VII-1: Treatment-Emergent AEs from CVT 3036 and GS-US-259-0116: Cardiac Arrhythmias and Conduction Abnormalities

	CVT 3036 (MERLIN-TIMI 36)		GS-US-259-0116 (RIVER-PCI)	
Preferred Term	Placebo (n = 3273)	Ranolazine (n =3268)	Placebo (n =1297)	Ranolazine (n =1322)
Tachyarrhythmia	3 (< 1%)	0	-	-
Tachycardia	13 (<1%)	12 (<1%)	6 (0.5)	5 (0.4%)
Ventricular arrhythmia	9 (< 1%)	4 (< 1%)	3 (0.2%)	0
Ventricular extrasystoles	37 (1%)	23 (<1%)	7 (0.5%)	9 (0.7%)
Ventricular fibrillation	12 (<1%)	12 (<1%)	(0.2%)	1 (0.1%)
Ventricular tachyarrhythmia	-	-	0	1 (0.1%)
Ventricular tachycardia	33 (<1%)	28 (1%)	6 (0.5%)	9 (0.7%)
Wolff-Parkinson-White syndrome	-	-	0	1 (0.1%)

Table S VII-2: Incidence of Clinically Significant Arrhythmias and ventricular Tachycardia of Eight Beats or More in High Risk Patients in Study CVT 3036

	Placebo	Ranolazine	*p*-Value
Number of Patients with Holter Data	3189	3162	
Incidence of clinically significant arrhythmias from 7-day Holter recording	2786/3189 (87.4%)	2525/3162 (79.9%)	<0.001
Number of patients with VT ≥ 8 beats from 7-day Holter recording	265/3189 (8.3%)	166/3162 (5.2%)	<0.001
Subgroup Analysis in Patients at High Risk of Developing Arrhythmias with VT ≥ 8 Beats			
TIMI Risk Score 5-7	58/654 (8.9%)	29/653 (4.4%)	0.001
Prior Heart Failure	51/547 (9.3%)	28/522 (5.4%)	0.013
LV Ejection Fraction ≤ 40%	48/289 (16.6%)	26/296 (8.8%)	0.004
QTc Interval at Baseline ≥ 450 ms	63/600 (10.5%)	33/591 (5.6%)	0.002

These clinical data indicate that ranolazine does not have proarrhythmic potential, which has been accepted in regulatory reviews worldwide during the review of the licensing application.

Post-marketing

A search was carried out in the Company Global Safety Database using the following search criteria:

Suspect drug	Ranexa (ranolazine)
Time period	Cumulative through 23 October 2016
Case criteria	Valid and invalid cases on the Gilead DSPH database: Spontaneous cases, solicited (non-clinical) cases, serious adverse events (SAE) reports from clinical trials.
Event(s) used to select cases for review	The following terms were selected from the Cardiac arrhythmia and Conduction defects Standard MedDRA Queries (SMQs) based on medical judgement: Arrhythmia Atrial fibrillation Atrial flutter Atrioventricular block Atrioventricular block complete Atrioventricular block first degree Atrioventricular block second degree Nodal arrhythmia Nodal rhythm Sinoatrial block Sinus arrest Sinus bradycardia Sinus node dysfunction Supraventricular tachycardia Torsade de pointes Ventricular arrhythmia Ventricular extrasystoles Ventricular fibrillation Ventricular flutter Ventricular tachycardia Sudden cardiac death Heart rate irregular Circulatory collapse
Database search date	24 October 2016

A total of 213 cases were retrieved from the company Global Safety Database. Eleven non-valid cases lacked sufficient information for assessment, and were excluded from the analysis. The remaining 202 cases included 101 medically-confirmed spontaneous cases, 5 literature cases, 66 solicited cases from the patient support program, and 30 serious adverse events (SAE) reports from clinical trials. Cases were grouped into related types of arrhythmia/conduction abnormalities (six groups) for the purpose of assessment of causality, as shown in Table S VII-3.

The majority of cases in this review either contained an alternative etiology for the reported event of arrhythmia/conduction abnormality, or contained insufficient clinical information from which to assess a causal association with ranolazine (see TableS VII-3).
In four cases (3 of atrioventricular [AV] block and one of sudden cardiac death), a lack of key data limited assessment of the case, however, these cases were not supportive of a causal association.
In the first case, first degree AV block (first occurred 36 days after initiating ranolazine) was reported to have resolved following the discontinuation of ranolazine. However, information was not provided on the action taken with concomitant metoprolol,

which is associated with first degree AV block (the interaction with metoprolol is mentioned in SmPC).
In a second case, key information is missing (medical history, risk factors for arrhythmia and event outcome), which reports AV block occurring 3 days after a dose increase of ranolazine (from 1000 mg to 2000 mg BID). The patient's advanced age (81 years), and underlying severe angina may have contributed to the event.
In the third case of AV block, the event occurred 4-8 hours after the first dose of ranolazine, after which ranolazine was discontinued with no recurrence of the event during the following 72 hours of monitoring. The advanced age of the patient (97 years), coronary artery disease and hypertension, may have contributed to the event.
In the final case, the etiology of sudden cardiac death was unclear. The patient's dose of Ranexa was increased from 500 mg to1000 mg BID due to worsening angina. Two days later, sulfamethoxazole/trimethoprim and a steroid injection were administered for an unknown indication. The patient died the following day from sudden cardiac death and no autopsy results were provided. The patient's worsening angina, ischemic heart disease, hypertension and hyperlipidemia may have contributed to the event.

Table S VII-3: Assessment of cases of cardiac arrhythmia/ conduction abnormalities

	Arrhythmias/conduction abnormities					
	AF, atrial flutter	AV block	Nodal rhythm and nodal arrhythmia	Sinus node dysfunction, sinus arrest, sinoatrial block	VF, VT, TdP, ventricular extrasystoles	Other arrhythmia & related events
Total number of cases[a]	61	22	5	6	67	52
Cases lacking key information preventing a clear causal assessment	-	3	-	-		1
Insufficient information to assess causality	27	11	-	-	21	32
Event not confirmed[b]	-	-	-	-	1	1
Alternative etiologies:						
Underlying cardiac disease	18	4	-	4	25	8
Concomitant medications	2	3	4	2	13 (QT interval prolonging conmeds n = 8)	6
Pre-existing disease	10	-	-	-	-	2
Evidence of other alternative etiologies[c]	4	1	1	-	7	2

Key: AF – atrial fibrillation, AV – atrioventricular block, VF – ventricular fibrillation, VT – ventricular tachycardia, TdP – Torsade de pointes.
a Cases containing more than 1 type of cardiac arrhythmia/conduction abnormality are included in each of the relevant analysis groups (n = 8)
b Event only speculative, or not confirmed by information provided in case.
c Includes cases with a negative dechallenge to drug, implausible time to event onset, or other significant risk factors for reported event

Risk factors and risk groups:
The term cardiac arrhythmia may be broadly defined as any abnormality or perturbation of the cardiac conduction system, including the sinoatrial (SA) node, atrioventricular (AV) node, bundle of His, and Purkinje fibers. A cardiac arrhythmia arises when there is an abnormality in either the initiation or conduction of the electrical pulses.
There are two broad classes of cardiac arrhythmias: bradycardias (also called bradyarrhythmias) and tachycardias (also called tachyarrhythmias), with each class consisting of multiple disorders (Li YR., 2015). Based on their origin, they are classified into supraventricular arrhythmias and ventricular arrhythmias, with arrhythmias that start in the atria or AV node being classified as supraventricular, whilst arrhythmias originating in the ventricles being classified as ventricular.
Cardiac arrhythmias are common disorder, and it is estimated that over 5 million Americans have one or more forms of cardiac arrhythmias, most over the age of 50 years. The general risk factors for cardiac arrhythmias include coronary artery disease, hypertension, metabolic disorders, smoking, consumption of alcohol, use of certain medication or elicit drugs (eg, amphetamines and cocaine), obesity, electrolyte imbalance, and old age. Genetic factors also contribute to certain arrhythmias, such as long QT syndromes (LQTS). The prevalence of cardiac arrhythmias increases with age, even when there's no clear sign of coronary artery disease.

Preventability:
The current EU SmPC, in addition to including prolonged QT interval as an adverse drug reaction in section 4.8 "Undesirable Effects", contains also the following statement:

- in the section 4.3 "Contraindications":

"Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone."

- in the section 4.4 "Special warnings and precautions for use":

"A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treatedwith drugs affecting the QTc interval."

- in the section 4.5 "Interaction with other medicinal products and other forms of interaction":

"There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g. imipramine, doxepin, amitriptyline)."

Impact on the risk-benefit balance of the product:
Considering the information from all sources analized during the post-marketing experience up to 23-Oct-2016, the actual impact of the risk is minimal. This risk will be kept under monitoring.

Public health impact:
Analysis of cases of arrhythmia and conduction abnormalities from the company global safety database revealed that the majority of cases either contain plausible alternative causes for the reported arrhythmia/conduction abnormality or contain insufficient information to assess causality. The remaining 4 cases, already discussed above (3 cases of AV block and 1 of sudden cardiac death) lack key information for a clear causal assessment.
The indication for ranolazine is, in most cases, a likely alternative explanation for any form of arrhythmia. The patient population who receive ranolazine are elderly and have coronary artery disease, both factors often associated with arrhythmic conditions, therefore the impact on public health of this disease/indication related issue is considered minimal.

SVII.3.2 Presentation of the missing information

Not applicable. No missing information is included in the safety concerns list.

PART II: MODULE SVIII. - **SUMMARY OF THE SAFETY CONCERNS**

Table S VIII–1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• QT prolongation
Important potential risks	• Myasthenic syndrome • Cardiac arrhythmias
Missing information	• None

PART III. : PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

All the safety concerns reported in this document (see Module II, part SVIII) are subjected to routine pharmacovigilance.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaire for "QT Prolongation" (important identified risk):

The aim of this questionnaire is to collect additional structured information about the description of the events and on clinical features of patients experiencing "QT Prolongation" to ranolazine (co-morbidities, concomitant medication usage, history of arrhythmias, history of congenital QT prolongation, electrolyte disturbances, or family history of sudden cardiac death). The form is provided in Annex 4 of this RMP.

- Other forms of routine pharmacovigilance activities for all safety concerns:

Not applicable.
A review of all safety concerns will be performed at each PSUR elaboration.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.
There are no ongoing or planned additonal pharmacovigilance activities in place for ranolazine products.

The study "MEN-RAN-303-IMS.001" was an IMS Disease Analyser study as part of the pharmacovigilance plan included in the ranolazine Risk Management Plan activity proposed at the moment of the centralised product registration filed by CVT Europe and thereafter inherited by MIOL when the MA was transferred from CVT to MIOL.
The IMS Disease Analyzer drug utilization study was a longitudinal patient database that provided information from Primary Care physicians and cardiologists on patient medical history, demographics, concomitant medication use, laboratory values and hospitalizations. This database had the ability to track patients' diseases and therapies over time, providing real world experience and valuable insight into what happened before, during, and after treatment with Ranexa by searching over 13.5 million patient records from approximately 2,500 office-based doctors in the UK, Germany, France, and Austria. Data have been obtained from the UK and Germany only, as Ranexa was not on the French market and the overall exposure in Austria was quite limited. The IMS Database searched for data originating from UK GPs, German GPs/Internists and Cardiologists. These data have been subjected to a series of quality checks to ensure consistent quality and completeness.

The IMS system was utilized to conduct study MEN-RAN-303-IMS.001 in order to detect and evaluate the ADRs associated with the use of ranolazine with the final aim to develop strategies to mitigate their occurrence.
The study was initiated after the product launch and the data were analyzed every 3 or 6 months. The interim results were discussed in each subsequent PSUR and the final results (collected from February 2009 to September 2012) were discussed in the EU PSUR#8 and presented in the Annex 4 of RMP version 7.2. The IMS Disease Analyzer was stopped after inclusion of 3,712 patients out of planned 10,000. However, according to the CHMP opinion adopted on 19 September 2013, the rapporteur did not request the reopening of the study.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing and planned additional pharmacovigilance activities for ranolazine.

Table Part III–1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
None	Not applicable	Not applicable	Not applicable	Not applicable

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.
There are no ongoing or planned imposed post-authorisation efficacy studies concerning ranolazine containing products.

PART V. : RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V–1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk: QT Prolongation	Routine risk communication: • **SmPC section 4.4:** Special warnings and precautions for use • **SmPC section 5.2:** Pharmacokinetic properties • **PL section 2:** What you need to know before you take ranolazine - Warning and precautions Routine risk minimisation activities recommending specific clinical measures to address the risk: •Recommendation to take caution on the treat of patient with history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval is included in SmPC section 4.4 • Warning on the use of ranolazine in patients that have ever had an abnormal electrocardiogram (ECG) is included in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Potential Risk: Myasthenic syndrome	Routine risk communication: • **SmPC section 4.8:** Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: - None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Potential Risk: Cardiac arrhythmias	Routine risk communication: • **SmPC section 4.3:** Contraindications • **SmPC section 4.4:** Special warnings and precautions for use • **SmPC section 4.5:** Interaction with other medicinal products and other forms of interaction • **SmPC section 4.8:** Undesirable effects • **PL section 2:** What you need to know before you take ranolazine - Do not take Ranexa - Warning and precautions - Using other medicines and Ranexa

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication on the administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone is included in SmPC section 4.3 • Recommendation to take caution on the treat of patient with history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval is included in SmPC section 4.4 • Recommendation on the concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias, is included in SmPC section 4.5 • Warning on the use of ranolazine in patients that have ever had an abnormal electrocardiogram (ECG) and to tell the doctor before taking ranolazine, if the patient uses certain medicines to treat allergies, heart rhythm disorders, and depression, as these medicines may affect the ECG. This information is included in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Not applicable: routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V–3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk: QT Prolongation	Routine risk minimisation measures: • **SmPC sections 4.4, 5.2** • **PL section 2** Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: Myasthenic syndrome	Routine risk minimisation measures: • **SmPC section 4.8** Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential risk: Cardiac arrhythmias	Routine risk minimisation measures: • **SmPC section 4.3** • **SmPC section 4.4** • **SmPC section 4.5** • **SmPC section 4.8** • **PL section 2** Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

PART VI. : SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR RANEXA®

This is a summary of the risk management plan (RMP) for Ranexa. The RMP details important risks of Ranexa, how these risks can be minimised, and how more information will be obtained about Ranexa's risks.

Ranexa's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ranexa should be used.

This summary of the RMP for Ranexa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ranexa's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Ranexa is authorised for add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists). It contains ranolazine as the active substance and it is given by oral administration as 375 mg prolonged-release tablets, 500 mg prolonged-release tablets and 750 mg prolonged-release tablets.

Further information about the evaluation of Ranexa's benefits can be found in Ranexa's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000805/human_med_001009.jsp&mid=WC0b01ac058001d124

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Ranexa, together with measures to minimise such risks and the proposed studies for learning more about Ranexa's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size -the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, the frequency of PSUR submission is currently revised to 3 years and it should be submitted within 90 days of the data lock point published in the updated list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of important risks and missing information

Important risks of Ranexa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ranexa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• QT prolongation
Important potential risks	• Myasthenic syndrome • Cardiac arrhythmias
Missing information	• None

II.B. Summary of important risks

Important identified risk: Heart rhythm disorder that can potentially cause fast abnormal heartbeats (QT Prolongation)	
Evidence for linking the risk to the medicine	Based on the published literature, a background of major cardiac events such as Torsade de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac death is expected in the general population, with an obvious increase in the prevalence of these events in patients with history of cardiovascular diseases, regardless of ranolazine treatment. Rather, ranolazine has shown a protective effect on some of these events. Based on these information, QT prolongation has been classified as Important Identified Risk.

Important identified risk: Heart rhythm disorder that can potentially cause fast abnormal heartbeats (QT Prolongation)	
Risk factors and risk groups	In patients with a combination of some factors (as concomitant treatment with drugs for abnormal heartbeats or history of congenital or a family history of abnormal heartbeats), along with others such as electrolyte disturbances, female gender, family history of ventricular arrhythmias or early sudden cardiac death, risk of serious events may be increased.
Risk minimisation measures	Routine risk minimisation measures: • **SmPC sections 4.4, 5.2** • **PL section 2** Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Group of conditions characterized by muscle weakness that worsens with physical exertion (Myasthenic syndrome)	
Evidence for linking the risk to the medicine	Epidemiological population-based studies as well as post-marketing data, have suggested to evaluate the risk of myasthenic syndrome with the use of ranolazine as Important Potential Risk.
Risk factors and risk groups	Women are twice as likely as men to be affected by myasthenia gravis. Onset of this disease can occur at any age; however, women under the age of 40 years and men over the age of 60 years are most commonly affected.
Risk minimisation measures	Routine risk minimisation measures: • **SmPC section 4.8** Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Disorders of heart rhythm (Cardiac arrhythmias)	
Evidence for linking the risk to the medicine	This issue has been considered as important potential risk due to the fact that in two studies, the events related to some of disorders of heart rhythm, were reported with higher number in patients treated with ranolazine compared to the patients treated with placebo.
Risk factors and risk groups	Disorders of heart rhythm are common. The general risk factors for an abnormal heart rithm include cardiac disease, increase in blood pressure, diabetes, smoking, consumption of alcohol, use of certain medication or elicit drugs (eg, amphetamines and cocaine), obesity, electrolyte imbalance, and old age.

Important potential risk: Disorders of heart rhythm (Cardiac arrhythmias)	
Risk minimisation measures	Routine risk minimisation measures: • **SmPC section 4.3** • **SmPC section 4.4** • **SmPC section 4.5** • **SmPC section 4.8** • **PL section 2** Additional risk minimisation measures: No risk minimisation measures

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ranexa.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Ranexa.

PART VII. : ANNEXES

Annex 1: EudraVigilance Interface *(Not applicable)*
Annex 2: Tabulated summary of planned, on-going and completed pharmacovigilance study programme
Annex 3: Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan *(Not applicable)*
Annex 4: Specific adverse drug reaction follow-up formsAnnex 5: Protocols for proposed and on-going studies in RMP part IV *(Not applicable)*
Annex 6: Details of proposed additional risk minimisation activities *(Not applicable)*
Annex 7: Other supporting data (including referenced material)
Annex 8: Summary of changes to the risk management plan over time

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

FOLLOW-UP FORMS

Print Form

Torsades de Pointes/ Ventricular Tachycardia/Sudden Death Targeted Follow-Up Questionnaire

Patient Initials	Date of Birth (DD/MM/YYYY)	Age (Years)	Weight ☐ Kg ☐ Lbs	☐ Male ☐ Female	MCN#

Description of the event

- What was the event? ☐ Monomorphic VT ☐ Polymorphic VT without QT prolongation ☐ Torsades de Pointes ☐ Sudden Death
- Event onset date (DD/MM/YYYY) ____/____/____ Hospitalization dates ____/____/____ to ____/____/____

Medication	Dosage	Start Date (DD/MM/YYYY)	Stop Date (DD/MM/YYYY)
Ranexa?			
Co-suspect Medication, including drugs with QT prolongation potential (Drug:_____)			

- Please describe the event, including patient activity at time of onset, any recent changes in medications prior to event, relevant concomitant medications, clinical course, diagnosis, and outcome. Please attach hospital discharge summary if available.

- If fatal, was an autopsy performed? ☐ No ☐ Yes ➪ Please attach a copy of the report, with all patient identifiers blackened out for privacy.
- Did the event occur following ☐ start of Ranexa ☐ increase in Ranexa dose ☐ addition of co-suspect drug ☐ increase in dose of co-suspect drug ☐ none of the above
- What treatment was administered for the event?
- Did the event occur during hospitalization for another medical condition? ☐ No ☐ Yes ➪ Reason for Hospitalization:_____
- What is the patient's left ventricular ejection fraction at baseline ? _____% (Please attach full ECHO report if available.)
- Please attach copies of ECG/rhythm strips and laboratory reports (with reference ranges), or provide a description of the ECG and labs, below.

Test date (DD/MM/YYYY)	Electrocardiogram (ECG)			Serum Potassium	Serum Magnesium	Blood Nitrogen(BUN)	Serum Creatinine	Serum AST	Serum ALT
	Heart rate	Heart Rhythm	PR/QRS/QTc intervals (msec)						
Baseline				☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____umol/L	☐Normal ☐Abnormal _____U/L _____U/L	☐Normal ☐Abnormal _____U/L _____U/L
At time of event				☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____mmol/L	☐Normal ☐Abnormal _____mg/dL _____umol/L	☐Normal ☐Abnormal _____U/L _____U/L	☐Normal ☐Abnormal _____U/L _____U/L

Patient's Cardiac/Medical and Family History (please check all that apply)

☐ Ischemic heart disease ☐ History of CHF ☐ Cardiomyopathy ☐ Valvular heart disease ☐ Genetic arrhythmia (eg. LQTS, Brugada's)
☐ Prior cardiac surgery ☐ Syncope ☐ QT prolongation ☐ Arrhythmia ☐ Bradycardia ☐ Other
☐ Hepatic Insufficiency ☐ Hepatic Cirrhosis ☐ Renal Impairment ☐ Chronic Renal Failure ☐ Renal Dialysis
☐ Family history of LQTS ☐ Family history of ventricular arrhythmias ☐ Family history of Sudden Death

Please provide details for checked items, if known:

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.