Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ranolazine

Proprietary Product Name: Ranexa

Sponsor: A Menarini Australia Pty Ltd

March 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au> .

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
5-HT	Serotonin
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACTH	Adrenocorticotrophic hormone
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse event
AF	Atrial fibrillation
AP	Action potential
APD	Action potential duration
AST	Aspartate aminotransferase
ATX-II	Anemone Toxin II
AUC	Area under the plasma concentration-time curve over one dosing interval
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0\text{-t}}$	Area under the plasma concentration-time curve from time 0 to last measurable time-point
AUC_{τ}	Area under the plasma concentration versus time curve over the dosing interval
AV	Atrioventricular
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical Classification System
BD	Twice daily
BE	Bioequivalence
BP	Blood pressure
CAD	Coronary artery disease
CCDS	Core company data sheet

Abbreviation	Meaning
CEC	Clinical Events Committee
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Oral clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	steady-state C_{max}
C_{min}	minimum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CV	coefficient of variation
CVT	CV Therapeutics, Inc.
CYP	Cytochrome P450
DMA or DMA 2,6	Dimethylaniline, or 2,6-xylidine
DSM	DSM Pharmaceuticals
EAD	Early after depolarization
ECG	Electrocardiogram
ER	Extended-release
ETT	Exercise treadmill (tolerance) testing
EU	European Union
FAS	Full analysis set
GLP	Good laboratory practice
GI	Gastrointestinal
GVP	good pharmacovigilance practices
h	Hour/s

Abbreviation	Meaning
HbA1c	Haemoglobin A1c
hERG	Human ether-à-go-go-related gene encoding pore-forming protein representing α-subunits of the human potassium channel responsible for IKr
HFpEF	Heart failure with preserved ejection fraction
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPLC	High performance liquid chromatography
HR	Heart rate
IARC	International agency for research on cancer
IC_{50}	50% inhibitory concentration (measurement of relative potency of inhibition)
ICa	Inward calcium current through L-type calcium channels
IK	Total delayed rectifier potassium current
IKr	Rapid delayed rectifier potassium current
IKs	Slow delayed rectifier potassium current
INa	Sodium channel current
INa-Ca	Sodium-calcium exchange current
IR	Immediate-release
IP	Intra peritoneal
ISD	Integrated Safety Database
ITT	Intent-to-treat
IV	Intravenous
IVIVC	In vitro in vivo correlation
K^+	Potassium ion
KA	Absorption rate constant
KM	Michaelis-Menten Constant, concentration corresponding to one-half the maximum elimination rate KvLQT1 Gene encoding pore-forming protein representing α-subunits of the human potassium channel responsible for IKs

Abbreviation	Meaning
LAN	Long-acting nitrate
LOCF	Last observation carried forward
LQT	Long QT syndrome
LV	Left ventricular
LVEDP	LV end-diastolic pressure
MDCK	Madin-Darby canine kidney cells
MDR	Multi-drug resistance
METs	Metabolic Equivalent of Task
MRHD	Maximum recommended human dose
MI	Myocardial infarction
min	Minute/s
mm Hg	Millimetres of mercury
NLT	Not less than
NMT	Not more than
NOEL	No observable effect level
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
PAC	Patient alert card
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Product information
PK	Pharmacokinetic
po	Per os (orally)
PR	Prolonged-release

Abbreviation	Meaning
PSUR	Periodic safety update report
PT_{max}	Maximum prothrombin time
QD	Once daily
QOL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval using Fridericia correction for heart rate ($QT/RR^{1/3}$)
RAN	Ranolazine
RER	Respiratory exchange ratio - the difference between resting and exercise RER from baseline to Day 14
RMP	Risk Management Plan
RPP	Rate pressure product
RS43285	Ranolazine
SAE	Serious adverse event
SAQ	Seattle Angina Questionnaire
SD	Standard deviation
SR	Sustained-release
t½	Terminal elimination half life
T2DM	Type 2 diabetes mellitus
TdP	Torsades de pointes
TDR	Transmural dispersion of repolarisation
TDS	Three times daily
TIMI	Thrombolysis in Myocardial Ischemia
T_{max}	Time to reach the maximum plasma concentration
TTC	threshold of toxicological concern
ULN	Upper limit of normal
V/F	Apparent volume of distribution

Abbreviation	Meaning
VE/VCO_2	Ventilation/carbon dioxide production ratio - the change from baseline in the difference between resting and exercise values for VE/VCO_2 at Day 14
Vmax	Maximal upstroke velocity
VT	Ventricular tachycardia

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	12 May 2016
Date of entry onto ARTG	13 October 2017
Active ingredient:	Ranolazine
Product name:	Ranexa
Sponsor's name and address:	A Menarini Australia Pty Ltd Level 8/67 Albert Avenue Chatswood NSW 2067
Dose form:	Modified release tablet
Strengths:	375 mg, 500 mg and 750 mg
Container:	Blister pack
Pack sizes:	15 and 60
Approved therapeutic use:	*Ranexa is indicated in adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control.*
Route of administration:	oral
Dosage:	375 mg twice daily as initial dose with amendment according to the patient's response. For full details please see the Product Information
ARTG numbers:	236110, 236108, 236109

Product background

This AusPAR describes the application by A Menarini Australia Pty Ltd (the sponsor) to register Ranexa, ranolazine 375, 500 and 750 mg modified release tablets for the following indication:

> *Ranexa 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 anti-angina therapies (such as beta-blockers and/or calcium antagonists).*

Angina occurs when myocardial oxygen demand exceeds supply. Demand is typically increased by exercise (especially isometric) or emotion. Oxygen supply is restricted by atherosclerotic obstruction of the coronary arteries and anaemia. The pain of stable angina is typically transient, lasting less than 10 minutes, and subsides promptly with rest. The pain usually bears a predictable relationship to walking and other activities involving physical effort or emotional stress. The aims of continuing therapy to prevent symptoms of angina are to reduce myocardial oxygen demand and increase oxygen supply, increase effort tolerance, and prevent the development of symptoms and complications. The usual treatments include beta-blockers (atenolol or metoprolol), non-dihydropyridine calcium channel blockers (diltiazem, verapamil) which reduce heart rate and can be used as an alternative to a beta blocker if the patient has a contraindication to beta blockade.

Ranolazine is a novel small molecule of a new pharmacological class which is believed to have its anti-ischaemic and antianginal effects via inhibition of the late sodium current in cardiac cells with a resultant reduction of intracellular sodium and intracellular calcium overload. The clinical development programme for ranolazine commenced in 1985 with initial studies using intravenous (IV) and immediate release (IR) formulations. In order to maintain an effective plasma concentration, an extended release (ER) formulation was developed. There have been sponsorship and formulation changes subsequently. A prolonged release (PR) formulation has been proposed for registration.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 13 October 2017.

At the time the TGA considered this application; a similar application had been approved, withdrawn or was under consideration in the countries as outlined in Table 1.

Table 1: International regulatory status

Country	Date submitted Date approved	Indications
European Union centralised procedure	Approved 9 July 2008	Ranexa 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).
USA	Approved 27 January 2006	Ranexa is indicated for the treatment of chronic angina.

Country	Date submitted Date approved	Indications
Canada	NA	NA
New Zealand	Submitted 24 November 2014	Same as EU
Singapore	Submitted 26 March 2014 Approved 6 October 2015	Same as EU
Switzerland	Submitted 4 June 2009 Approved 13 April 2010	Same as EU
Australia	Submitted 8 December 2009 Withdrawn by sponsor (Gilead Sciences in mid-2011)	Ranexa is indicated for the treatment of chronic angina. (500 mg and 1000 mg strengths applied for only). Sponsor unable to provide a full and complete response in the timeframe required, in relation to the impurity method and method validation.
Taiwan	Submitted 10 February 2014 Withdrawn by the sponsor Sponsor unable to provide enough efficacy and safety data on local population	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).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2: Registration timeline for submission PM-2015-00423-1-3

Description	Date
Submission dossier accepted and 1st round evaluation commenced	29 May 2015
1st round evaluation completed	2 November 2015
Sponsor provides responses on questions raised in 1st round evaluation	4 January 2016
2nd round evaluation completed	26 February 2016

Description	Date
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	2 March 2016
Sponsor's pre-Advisory Committee meeting response	14 March 2016
Advisory Committee meeting	1 April 2106
Registration decision	12 May 2016
Entry onto ARTG	13 October 2017
Number of TGA working days from submission dossier acceptance to registration decision *	197

*Statutory timeframe: 255 working days

III. Quality findings

Introduction

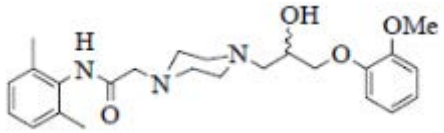
The current submission is a re-submission of a previous (2009) application by Gilead Sciences Pty. Ltd to register 500 mg and 1000 mg modified (prolonged) release ranolazine Ranexa tablets (submission PM-2009-03573-3-3). The submission was ultimately withdrawn and some quality issues remained unresolved [notably adequate control of the potentially genotoxic degradant 2,6-dimethylanaline (DMA)]. The tradename and formulations of the 500 mg tablets are identical in each case, although tablet marking differ. In this submission the company has included justifications addressing deficiencies in the previous Ranexa submission.

Ranolazine is formulated as sustained release tablets to achieve convenient daily coverage, as ranolazine has a relatively short elimination half-life of 2 hours. The proposed release mechanism of the tablets is unusual in using a pH sensitive methyl- and ethyl- acrylate copolymer as matrix combined with hypromellose as tablet binder which also retards release.

The recommended initial dose of Ranexa is 375 mg twice daily. After 2 to 4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to the recommended maximum dose of 750 mg twice daily. The PI includes instructions that the tablets are to be swallowed whole with food, and are not to be crushed, broken or chewed.

Drug substance (active ingredient)

Figure 1: Ranolazine structure



The drug substance contains a single chiral centre and is presented as the racemate.

- pKa: 2.2 and 7.2
- Solubility; pH dependent: 143 mg/mL at pH 3.4, 41 mg/mL at pH 5.0 and 0.4 mg/mL at pH 7.0
- Biopharmaceutical Classification System (BCS) Class 4 (high solubility, low permeability).

Ranolazine is prepared completely by chemical synthesis in a 3 step process which yields the racemic material.

The route of synthesis leads to a single crystalline polymorphic form of the non-solvated material (Form I). Two other polymorphs and an amorphous form have been generated, but are not formed in the proposed process. A melting point test ensures the presence of the correct polymorph.

The specification for ranolazine drug substance includes satisfactory limits for assay (98.0 to 102.0%) and particle size distribution.

Four potential organic impurities have been identified in ranolazine for which appropriate limits are included in the drug substance specifications. The Impurity GGE (Ran3) is an epoxide and is potentially genotoxic. Consequently much tighter limits are proposed not more than (NMT) 0.75 ppm, the threshold of toxicological concern (TTC), for the product), measured by a separate sensitive high performance liquid chromatography (HPLC) method using fluorescence detection. Limits imposed for residual solvents ethanol and toluene are lower than the ICH limits.

The proposed drug substance specifications are considered adequate to ensure the quality and consistency of the manufacture of the finished product.

The drug substance shows good solid state stability and adequate stability data have been provided to support a retest period for the drug substance of 5 years stored below 25°C.

Drug product

The drug product is presented in three dosage strengths as film-coated, biconvex, prolonged release (PR) tablets. The three dosage strengths have the following appearances:

- 375 mg tablet: pale blue debossed with “375” on one side and plain on the other side
- 500 mg tablet: light orange debossed with “500” on one side and plain on the other side
- 750 mg tablet: pale green debossed with “750” on one side and plain on the other side

The 500 mg tablets are essentially identical (apart from tablet markings) to the tablets proposed in the previous Ranexa submission. The previously proposed 1000 mg tablets

are not included in the current submission. The tablets are to be manufactured by a single site.

The cores of the three strengths are direct scales manufactured by wet granulation, drying milling and compression. The granulation is well controlled to give a consistent particle size distribution.

The extended release properties of the tablets are imparted by the excipients methacrylic acid-ethyl acrylate copolymer 1:1 and hypromellose. On contact with water these form a polymeric matrix through which water must diffuse to dissolve and release the drug substance. The solubility of this matrix is pH dependent; being insoluble at low pH and soluble above pH 5. Thus in relation to dissolution, there are two competing factors: the solubility of the drug substance decrease as pH increases and the release rate from the polymeric matrix increases as the pH increases. Thus as pH increases from the pH 1.2 to pH 7, the dissolution rate decreases and then increases again to higher than at pH 1.2. This effect of pH was brought to the attention of the Delegate as it might affect the bioavailability for achlorohydric patients (although data suggests that a modest (approximately 5%) slowing of dissolution rate at the 4 hour test point won't significantly affect the bioavailability).

The dissolution performance was also slowed in the presence of ethanol but this does not lead to dose dumping. In fact the dissolution rate decreases slightly as the ethanol concentration increases. This slowing of dissolution does (just) lead to a failure to meet the dissolution limit at 20 hours. This was brought to the attention of the Delegate for consideration as to whether a statement in the PI is warranted.

The specifications have acceptable expiry limits and identical release limits (this is acceptable as no changes occur on storage). Thus:

- The assay limits are 95.0 to 105.0%, in-line with TGO 78.
- The dissolution medium was justified and separate limits were proposed for the 375/500 mg and the 750 mg tablets reflecting tablet size effects on release rates.

The dissolution specifications were set based on dissolution of lots used in pivotal clinical/bioavailability studies and the limits at each sampling time (0.5 hour, 4 hours, 12 hours and 20 hours /24 hours) are based on the guidance requirements.[1]

For the two lower strength tablets, data from only 500 mg MR tablets were used in arriving at the acceptance criteria. The acceptance criteria for the 500 mg tablet are also proposed for the 375 mg tablet. Dissolution data for the 375 mg tablet were not included in the dataset used to establish the acceptance criteria because the 375 mg tablet was not used in any of the pivotal clinical studies or the bioequivalence (BE) study CVT 301-15. This is acceptable and it is noted that the Level 1 limits proposed are the same as were proposed and found acceptable for the 500 mg tablets in the previous Ranexa submission.

For the 750 mg tablet, limits are based on the 1000 mg tablet (not proposed in this submission), which was used in bioequivalence (BE) study CVT 301-18. Dissolution data for the 750 mg tablet were not included in the dataset used to establish the acceptance criteria because the 750 mg tablet was not used in any pivotal clinical or bioavailability study. The acceptance criteria for the 1000 mg tablet will also be applied to the 750 mg tablet. The 750 mg and 1000 mg tablets have the same composition and similar dissolution profiles in various pH media; these data have been used to support waiving a BE study for the 750 mg tablet. This approach to setting dissolution limits is acceptable and it is noted that the Level 1 limits proposed are the same as were proposed and found acceptable for the 1000 mg tablets in the previous Ranexa submission, except for the final

[1] CPMP/QWP/604/96 Note for Guidance on Quality of Modified Release Products

time point which was changed to 24 hours at the request of the FDA and tightened to not less than (NLT) 80%.

In the previous submission of Ranexa, dissolution testing was limited to Level 1 only and the sponsor provided an assurance that only product passing the dissolution test at Level 1 will be supplied to Australia. In the current submission, the sponsor submitted an acceptable justification for the application of Level 2 and 3 testing.

All individual degradants are limited to NMT 0.10% and total degradants to NMT 0.2%, in line with the ICH identification and qualification thresholds.

The company submitted a detailed justification concerning testing of the genotoxic impurity/degradant 2,6-dimethylanaline (DMA) since the lack of a specific test and limit for this substance in the finished product was a major deficiency of the previous Ranexa submission. The company has demonstrated, using a new, validated LC-MS/MS test method, that DMA is typically present at very low levels in the tablets (0.7 to 0.9 ppm; versus toxicologically acceptable limit of 13.6 ppm). They have agreed with the TGA's request to include a specific test and limit for DMA content in the finished product specifications (NMT 4 ppm at release and NMT 12 ppm at expiry). The test will be performed every 6 months and the need for the test will be re-assessed after 5 years. This is considered acceptable.

The chemistry and quality control aspects of the PI have been finalised to the satisfaction of the quality evaluator, as have the carton and blister foil labels and the provisional ARTG Records.

The tablets show good stability and a shelf life of 24 months when stored below 25°C, in the original packaging, has been justified.

Biopharmaceutics

This submission included seven bioavailability studies, of which three have been previously evaluated or summarised during the previous Ranexa submission:

- Study CVT 301-14: The presence of an in vitro in vivo correlation (IVIVC) was investigated, together with the relative bioavailability compared to an oral solution.
- Study CVT 301-15: The bioequivalence of commercial scale tablets to the pilot scale tablets used in the Phase III clinical efficacy studies was investigated.
- Study CVT 301-18: The relative bioavailability of the 500 mg and 1000 mg tablets was investigated.

Brief summaries of these are reproduced below.

Of the remaining four studies, three were considered to be not relevant as they involved manufacturing sites not relevant to this submission, have been superseded by later studies or only involved irrelevant dosage forms (IR capsules) and were consequently not evaluated.

The remaining study (RAN-0122) investigated the dose proportionality of the 375 mg and the 750 mg PR tablets and is summarised below.

The 500 mg tablet used in Phase III clinical efficacy studies was of the same formulation as that proposed for registration except that it had a different film-coat. Below this is termed the 'old' formulation. Comparative dissolution data was provided to show the dissolution performance was not affect by the film-coat and it is accepted that the 500 mg tablet

proposed for registration (termed 'new' formulation) is bioequivalent to the 500 mg tablet used in the Phase III clinical efficacy studies.[2]

Previously evaluated studies

The levels of ranolazine in plasma were determined using either an HPLC method with MS/MS detection after protein precipitation with acetonitrile/methanol or a different HPLC method with fluorescence detection. Adequate validation data for these methods were provided. Neither of the methods were enantio-specific, but it was stated that interconversion of the enantiomers did not occur in vivo.

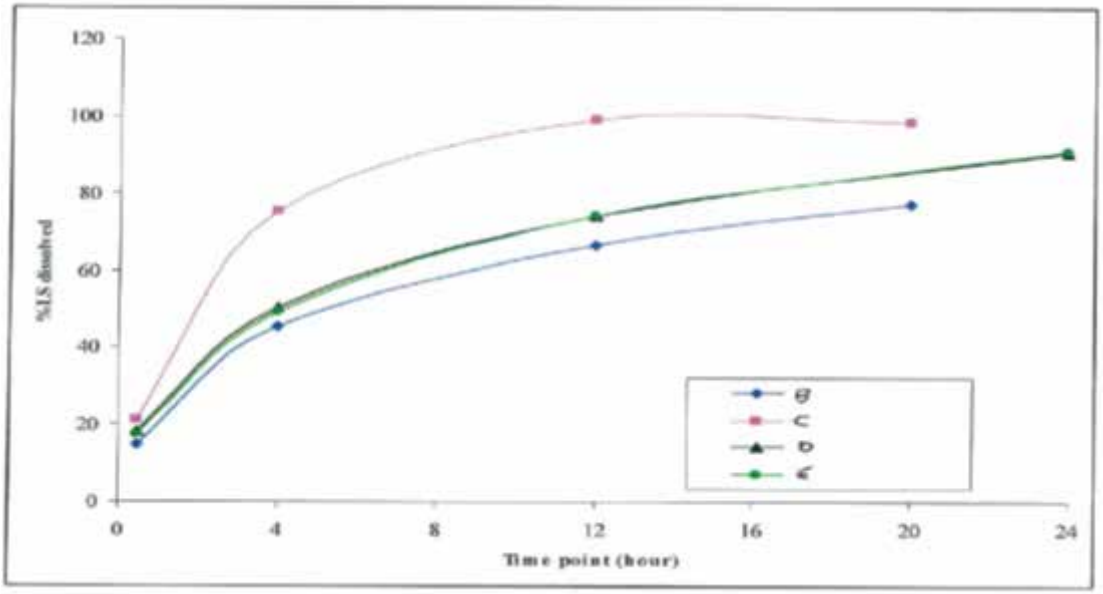
Study CVT 301-14

This was a single dose, five way cross over study in 16 subjects (15 completed as one was withdrawn due to a protocol violation) to investigate the presence of an IVIVC and the relative bioavailability compared to an oral solution. The five treatments were:

- Treatment E was the 'old' formulation 500 mg tablet from the (previously) proposed site of manufacture.
- Treatment D was a 500 mg tablet with the same core as Treatment E, but a blue film coat rather than an orange film coat.
- Treatment C was a 500 mg core only. It contained less methacrylic acid-ethyl acrylate copolymer to make it much faster to dissolve.
- Treatment B was a coated 500 mg tablet. It contained more methacrylic acid-ethyl acrylate copolymer to make it slightly slower to dissolve. The film coat was pink rather than orange.
- Treatment A was a 25 mg/mL oral solution.

The dissolution results for the tablets in 0.1N HCl are given below.

Figure 2: Dissolution profiles of ranolazine tablets in 0.1 N HCl



The bioavailability results (see below) indicate treatments B and D are both bioequivalent (with respect to AUC[3]) to treatment E, but that the faster dissolving treatment C has lower bioavailability.

[2] Note Study CVT 301-14 also indicated that the film-coat had no effect on bioavailability.

Table 3: Assay normalised results and confidence intervals from Study CVT 301-14

Parameter	Treatment B	Treatment C	Treatment D	Treatment E
C_{max} (µg/mL)	0.94	0.47	0.95	0.97
AUC_{0-t} (µg.h/mL)	8.8	6.7	8.1	8.0
90% CI C_{max}	0.78-1.15	0.39-0.57	0.83-1.23	na
90% CI AUC_{0-t}	0.83-1.23	0.63-0.93	0.83-1.22	na

[a] Normalised to an assay of 102.6% e.g. The results for Treatment E are unchanged and the results for Treatments B-D have been increased by the appropriate factor as the assays were 97.9, 98.2 and 101.8%.

The company calculated that there was no Level A IVIVC between the dissolution results and the pharmacokinetic profiles obtained from the study and this was accepted. However there does appear to be a Level C IVIVC between the amounts dissolved in 0.1 M HCl at 4 hours and both the maximum plasma concentration (C_{max}) and AUC_{0-t}[4] results obtained. This information was used to set appropriate dissolution limits.

The results also indicate that the 'old' formulation 500 mg tablet from the proposed site of manufacture has a relative bioavailability of 76% that of an oral solution.

Study CVT 301-15

This was a six period, three treatment, single dose replicate cross over study in 36 subjects (35 completed as one withdrew consent after two doses). The study was of an appropriate design using the 'old' formulation 500 mg tablets: two treatments were those used in the CARISA and MARISA Phase III clinical efficacy studies (these were manufactured on a smaller scale at different site of manufacture to that proposed for the commercial product); and the other was product from the proposed site of manufacture.

The results indicate that the 500 mg tablets used in the Phase III clinical efficacy studies and the 'old' formulation 500 mg tablets manufactured at the proposed site of manufacture are bioequivalent.

Study CVT 301-18

This was an eight period, four treatment, single dose replicate cross over study in 44 healthy subjects (35 completed as one was withdrawn due to an adverse event, one failed the urine test, and seven for various administrative reasons). The study was of an appropriate design and compared 'old' formulation 500 mg ER tablet to the proposed formulation 1000 mg ER tablet (and two other test 1000 mg ER tablets) at a dose of 1,000 mg.

The results indicate that proposed formulation 1000 mg ER tablet is bioequivalent to the 'old' formulation 500 mg ER tablet (the 90% confidence intervals were 0.93 to 1.07 for AUC and 0.94-1.12 for C_{max}).

Submitted, relevant Bioavailability study, not previously evaluated

Study no. RAN-0122

A multiple dose study to assess the comparative bioavailability of ranolazine Sustained-release (SR) administered as either two 375 mg tablets or one 750 mg tablet given twice daily in 30 young, healthy male subjects.

Study RAN0122 was an early study (1994) carried out to assess the comparative bioavailability of ranolazine PR tablets (manufactured at the development site) when

[3] AUC = Area under the plasma concentration-time curve over one dosing interval
[4] AUC_{0-t} = Area under the plasma concentration-time curve from time 0 to last measurable time-point

administered as either two 375 mg tablets or as one 750 mg tablet and to determine whether they are bioequivalent. It remains relevant to the current submission as the core formulations are identical to the proposed tablets, although they have a different film-coat composition.

Analytical method for determination of ranolazine in plasma (HPLC with fluorometric detection following solid phase extraction) has been appropriately validated. Conduction of study is considered appropriate.

The study was a multiple dose, open label, randomised two way crossover design study. Subjects received multiple oral doses of 750 mg ranolazine SR, as either two 375 mg tablets (2 x ranolazine 375 mg) or as one 750 mg tablet (ranolazine 750), twice daily tor 4 days with a single dose on Day 5. Each phase was separated by a washout period of at least 6 days. On Day 5 of each phase, ranolazine plasma concentrations were measured at specified time points during the 12 hour period following dosing.

Reported pharmacokinetic parameters and statistical analyses

Table 4: Day 5 mean ± standard deviation (SD) ranolazine SR pharmacokinetic parameters (n = 30)

Parameter	2 x RAN 375	RAN 750	90% CI for ratio of geometric means
Cmax (ng/ml)	2533 ± 1005	2359 ± 940	98.8%, 117.8%
Median Tmax (h)	4.00	5.00	-
Cmin (ng/ml)	1015 ± 673	981 ± 608	90.1%, 116.9%
AUC96-108h (ng.h/ml)	21782 ± 10279	20204 ± 9236	98.8%, 116.7%
Cave (ng/ml)	1815 ± 857	1684 ± 770	98.8%, 116.7%
Degree of Fluctuation	0.908 ± 0.247	0.880 ± 0.252	95.0%, 112.1%

Conclusion

Following multiple oral doses of ranolazine SR, administered as either 2 x 375 mg SR tablet or as one 750 mg SR tablet, the 90% confidence intervals for the ratio of the mean pharmacokinetic parameters were all within the 80 to 125 % limits for log transformed data indicating that the two treatments are bioequivalent.

Two justifications for the absence of bioequivalence data were submitted:

- Justification for Absence of absolute bioavailability data for the proposed prolonged release formulation

  The initial bioavailability studies (RAN009 and RAN019) determined the absolute bioavailability of ranolazine using the immediate release and oral solution formulations.

  The relative bioavailability of the prolonged release formulation versus the immediate release formulation and the oral solution was then assessed in several crossover studies (RAN066, RAN067, RAN0102, and CVT 301-14).

This justification is considered acceptable.

- Justification for not providing Bioequivalence Studies for 375 mg and 750 mg Tablets

  The proposed commercial 500 mg and 1,000 mg tablets have been demonstrated to be bioequivalent to tablets used in the Phase III clinical trials.

An assessment of bioequivalence of the 375 mg and 750 mg tablets are considered not necessary as these products are sufficiently similar to the 500 mg and 1000 mg tablets in terms of composition, dissolution specifications and in vitro dissolution profile.

This justification is considered acceptable since all tablets are direct scales and are the same shape and the available bioavailability results for the 500 mg and 1000 mg tablets are also considered relevant to the 375 mg and 750 mg strength.

Quality summary and conclusions

All pharmaceutical chemistry and quality control issues raised during the initial evaluation of this application have been satisfactorily resolved.

Registration of the proposed Ranexa ranolazine 375 mg, 500 mg and 750 mg modified release ranolazine tablets, all to be supplied in PVC/PVDC/Al blisters in packs of 15 tablets or 60 tablets, is recommended with respect to quality and biopharmaceutic aspects.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the ACPM, in keeping with recent branch policy. However, the previous Ranexa submission (2009-03573-3-3) was presented to the Pharmaceutical Subcommittee of ACPM (PSC) in Sept 2010.

Recommendations of the ACPM (PSC) meeting September 2010 (for submission PM-2009-03573-3-3):

1. There should be no objection on pharmaceutic and biopharmaceutic grounds to approval of the application by Gilead Sciences Pty Ltd to register RANEXA modified release tablets containing 500 mg and 1000 mg of ranolazine provided all outstanding issues are addressed to the satisfaction of the TGA.
2. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues. In particular;
   - The committee supports the evaluator's questions in relation to enantiomers, the active metabolites, the impact of ethanol on dissolution and the IVIVC data.
   - The committee supports the evaluator's questions in relation to the dissolution test method and limits.
   - The committee agreed that further stability data was required on production scale batches before a shelf life can be assigned.
3. The PSC agreed that the population pharmacokinetic analysis supports the sponsor's conclusion in relation to the clinical development of the product.

IV. Nonclinical findings

Introduction

A Menarini Australia Pty. Ltd. has applied to register the new chemical entity ranolazine (Ranexa). Ranolazine is indicated for use in adults as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti–anginal therapies. Ranolazine is formulated as a prolonged release tablet at three strengths (375 mg, 500 mg and 750 mg) and is to be administered at up to 750 mg twice daily (1,500 mg/kg/day, PO).

PM-2015-00423-1-3 is a resubmission of a previous application (PM-2009-03573-3-3). The nonclinical data set is generally the same as that previously provided, with the

exception of a new in vitro study concerning the effects on uptake and efflux transporters (Study No. AD-259-2005). As well, the sponsor provided two toxicological risk assessment reports to justify the presence of 2,6 – dimethyl aniline as a non-specified impurity.

The nonclinical evaluation report was presented to the Delegate in two parts.

The first part is the evaluation presented for submission PM-2009-03573-3-3. The second part is an addendum for the current submission which includes assessment of additional data provided for the current submission (PM-2015-00432-1-3).

Nonclinical report for submission PM-2009-03573-3-3

Submission PM-2009-03573-3-3 was an application to register a new chemical entity ranolazine (Ranexa) as 500 mg and 1000 mg film coated prolonged release (PR) tablets, for the treatment of chronic angina in adults. The maximum recommended clinical dose is 1000 mg twice daily (BD) (total 2000 mg/day; equivalent to 40 mg/kg/day for a 50 kg person or 1336 mg/m^2/day).

Quality of the nonclinical dossier

An extensive set of pharmacology (primary, secondary and safety) were conducted, but many were conducted more than 20 years ago. Only one of the safety pharmacology studies was good laboratory practice (GLP) compliant, since most were conducted prior to GLP requirements being applicable. Despite deficiencies in the design of some studies sufficient data were submitted to allow a comprehensive evaluation of the pharmaco toxicological profile of ranolazine. Individual electrocardiogram (ECG) data were not submitted for any of the studies but were provided in summarised form. Key toxicity studies were GLP compliant, were conducted in appropriate species, and were generally of adequate duration (but see note under 'Carcinogenicity' below). Doses used in the nonclinical studies were limited by neurological signs such that the animal:human exposure ratios tended to be low. All the studies (with the exception of a preliminary study in dogs) were conducted using a non-slow release formulation. Some studies were conducted with the free base of ranolazine and while others used the dihydrochloride. All toxicity studies were conducted using the racemate while some of the pharmacology and pharmacokinetics studies used the separate enantiomers.

Pharmacology

The sponsor has suggested that ranolazine exerts its anti-ischaemic and anti-anginal effects by inhibiting the late sodium channel current (late INa) in cardiac cells, which is presumed to be mediated by the tetrodotoxin-sensitive Na^+ channel. The slowly inactivating Na^+ current (also referred to in this report as the persistent, sustained, or late INa[5]) is very small in normal myocardium and has no apparent physiological role. However, a reduction in late INa is thought to reduce intracellular sodium accumulation and consequently decrease intracellular Ca^{2+} overload, thereby reducing the effects of excess intracellular Na^+ on the electrical and mechanical function of the heart. Therefore ranolazine treatment is anticipated to reduce these intracellular ionic imbalances during ischaemia. Ultimately, reduction in cellular Ca^{2+} overload is expected to reduce myocardial

[5] Late INa is distinguishable from peak INa (although both pass through the same cardiac Na+ channels) by its lower amplitude and longer duration. Peak INa is of brief duration but is responsible for the initiation of the cardiac action potential. Late INa measured in isolated cells is stimulated by the presence of lysophosphatidylcholine, which accumulates during ischaemia, and is partly dependent on increased long-chain acyl carnitine.

stiffness, oxygen consumption, and ATP utilization, and to improve blood flow to the microvasculature.

Effect on late inward sodium current

There were no studies demonstrating the direct binding of ranolazine to Na^+ channels nor was there any useful comparison of ranolazine against other INa blockers such as flecainide. However, it was shown that ranolazine (and a number of its metabolites) significantly blocked the late INa, and binds to a single site in Nav1.5 channels. In in vitro electrophysiology studies, ATX-II was used to amplify the late INa, which normally is quite small. Evidence from these experiments, using dog cardiac myocytes as well as HEK293 cells expressing the Nav1.5 cardiac sodium channel, indicated that ranolazine inhibited the late INa with an 50% inhibitory concentration (IC_{50}) within a clinically relevant range (5 to 7 µM). Moreover, the effect of ranolazine on late INa block could be differentiated from its effects on peak INa. In the two studies referred to above the IC_{50} were ≥ 38 fold greater for the peak INa than for the late INa. However, the potency differential was considerably lower (2 to 3 fold) in other studies. Nevertheless, the greater effect on late INa than on peak INa was suggested by the sponsor to provide the basis for the absence of effect of ranolazine on conduction velocity in vivo.

The effects of ranolazine enantiomers and of 13 ranolazine metabolites (including those representing > 10% of the $AUC_{0\text{-}24\,h}$ of ranolazine in humans, based on Study CVT 303.001-MET; on late sodium current were investigated in one study using dog left ventricular myocytes (study CVT303.063-P). The activities of the relevant metabolites are shown in Table 5. These data show that the activity of the enantiomers was similar and that a number of the relevant metabolites also had significant late INa blocking activity, albeit less potent than ranolazine enantiomers.

Table 5: activities of the relevant metabolites

Compound/		Residual Fractional activity (1.000: no inhibition)	% inhibition
Metabolite or enantiomer (10 µM unless otherwise stated)	n	late Ina	late INa
S-ranolazine	5	0.524	47.6%
(S-ranolazine 3 µM)	4	0.873	12.7%
(S-ranolazine 30 µM)	5	0.087	91.3%
R-ranolazine	5	0.415	58.5%

Compound/		Residual Fractional activity (1.000: no inhibition)	% inhibition
(R-ranolazine 3 µM)	6	1.080	-
(R-ranolazine 30 µM)	5	0.254	74.6%
CVT-5432 (RS-88390 conjugate)	5	1.003	-
CVT-2738 (RS-94287)	6	0.772	22.8%
CVT-4786	6	0.917	8.3%
CVT-2514 (RS-88390)	5	0.636	36.4%
CVT-5431 (Ranolazine glucuronide)	5	0.857	14.3%
CVT-2512 (RS-88640)	6	0.998	-

Effect on [Ca^{2+}]i overload

Calcium overload triggers pathological events in the cell, such as arrhythmias, mechanical dysfunction and, eventually, cell death, and precipitates structural damage and functional failure in the ischemic and reperfused myocardium.[6]

Increases in intracellular Ca^{2+} elicited by ATX-II (an inducer of the late INa) in rat isolated ejecting hearts were reduced in the presence of ranolazine at clinically relevant concentrations (4 to 8 µM). Ranolazine was also shown to significantly reduce the increase in [Ca^{2+}]i resulting from ischaemia to approximately pre-ischaemic levels in rat hearts. However, ranolazine only weakly inhibited late ICa[7] (IC_{50} ≥ 50 µM) and had little effect on peak ICa and INa-Ca[8] (IC_{50} ≥ 90 µM) in cardiac electrophysiology studies. Ranolazine, its enantiomers, and its metabolites also had no significant binding to L-type Ca^{2+} channels in

[6] Ver Donck L, et al. Inhibition of sodium and calcium overload pathology in the myocardium: a new cytoprotective principle. *Cardiovascular Research*. 1993; 27: 349-357.
[7] Ica = Inward calcium current through L-type calcium channels
[8] INa-Ca = Sodium-calcium exchange current

the brain, and had no effect on L-type Ca^{2+} channel dependent contractility in rat isolated left atria.

Anti-ischaemic effects

Ranolazine and its enantiomers suppressed the ischaemia induced ECG changes indicative of contractile dysfunction in a canine model of reversible ischaemia (reduction in perfusate flow followed by reperfusion) as well as improving cardiac performance in a canine model where heart failure was induced by a series of microembolisations. These anti-ischaemic effects were seen at ranolazine concentrations as low as 0.3 μM. These effects were independent of any effects on heart rate (HR), arterial blood pressure (BP), left ventricular (LV) contractility, or systemic vascular resistance.

Adrenergic receptor blockade

Ranolazine was shown to bind to α1a, b and β1,2-adrenergic receptors with affinities (Ki) in the range of 5 to 20 μM, and to serotonin 5HT1A receptors with a Ki of 2 μM. Ranolazine, its S-enantiomer and three metabolites (RS-88390, RS-89961 and RS-88772) had a similar affinity for β1-adrenergic receptors, with the R-enantiomer having no significant binding. The affinity of these compounds for β2 receptors was slightly lower. Since the C_{max} at the maximum recommended clinical dose has been measured at 3.8 μg/mL (approximately 8 to 9 μM), it is possible that ranolazine may attenuate α1- and β1-adrenergic receptor mediated responses, and may have activity at the 5HT1A receptor at these concentrations. Nevertheless, it would appear that the anti-ischaemic and left ventricular(LV) function improvement effects of ranolazine in dogs were not simply due to α1- or β1-adrenoreceptor blockade as there was little effect on heart rate, arterial blood pressure, LV contractility or systemic vascular resistance at steady state concentrations up to 18 μM.

In secondary pharmacodynamics studies, ranolazine increased glucose-stimulated insulin release in rat pancreatic β-cells and improved glucose homeostasis during oral glucose tolerance testing in insulin-resistant (high sucrose diet) rats. The sponsor speculated that this may be mediated through inhibition of ion currents (for example, INa, IK[9]) in pancreatic β-cells resulting in a modulation of insulin release, but no direct evidence for this was presented.

Overall, while the sponsor has presented separate evidence for ranolazine blockade of late INa, reductions in myocardial $[Ca^{2+}]i$ overload, and various anti-ischaemic effects, the exact mechanism of action is still unclear. This is reflected in the "Mechanism of Action" statement in the PI.

Pharmacodynamic interactions

No significant haemodynamic interaction of ranolazine was seen in dogs with isosorbide dinitrate (a long-acting nitrate) or the phosphodiesterase-5 inhibitor, sildenafil.

Safety pharmacology

Only one of the safety pharmacology studies was GLP compliant. Moreover, many of the studies were conducted using experimental models which have not been validated. However, the overall extent and design of the cardiovascular safety pharmacology studies was in general accordance with the requirements of ICH S7B[10], including investigation of cardiovascular, gastrointestinal, neurological and pulmonary systems and the use of positive controls where appropriate. Therefore, despite significant deficiencies in

[9] IK = Total delayed rectifier potassium current
[10] ICH S7B The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals.

individual studies, sufficient data were submitted to characterise the safety pharmacology of ranolazine.

Cardiovascular effects

There was an appropriate focus on potential for torsadogenic (Torsades de pointes (TdP)) activity and pro-arrhythmic potential in the cardiovascular investigations.

At doses higher than those found effective in animal models of ischaemia and heart failure (generally ≥ 30 μM), ranolazine depressed BP, HR, coronary blood flow, contractility and systemic vascular resistance. Ranolazine, at concentrations greater than the maximum concentration anticipated at the recommended clinical dose, did not induce early after depolarisations (EADs) in a number of nonclinical models. In fact, at therapeutically relevant concentrations (≤ 10 μM), ranolazine suppressed EADs and/or triggered activity induced by other drugs (sotalol, quinidine, ATX-II, E-4031, Chromanol). However, at plasma concentrations ≤ 18 μM, ranolazine did not cause significant haemodynamic effects in some animal models. Ranolazine did not induce TdP in a model susceptible to drug induced polymorphic ventricular tachycardia (VT) at doses that prolonged the QT interval by up to 11%. Ranolazine did not cause statistically significant increases in transmural dispersion of repolarisation (TDR), and generally reduced the incidence of ventricular fibrillation that occurs upon reperfusion and re-oxygenation after ischaemia, hypoxia, or anoxia.

In vitro studies indicated a tendency to increase the QRS interval at ≥ 30 μM, but not at ≤ 10 μM. The comparator, flecainide, tended to increase this interval at lower doses. Inhibition of IKr[11] by ranolazine may have explained the prolongation of the action potential duration (APD) and QT interval in animal ventricular cells and in humans. A number of other drugs which have proarrhythmic effects block IKr. At concentrations that had little effect on the maximal upstroke velocity (V_{max})of the ventricular action potential (AP), ranolazine inhibited late INa with a potency 2- to 4 fold greater at the AP plateau (approximately 5 to 6 μM) than at Phase 3 of the AP (approximately 11 to 21 μM). Its inhibitory potency at Phase 3 depended on the frequency of depolarization. Inhibition of late INa by ranolazine therefore appeared to be both voltage and use dependent.

Consistent with receptor binding experiments which showed that ranolazine blocked adrenergic receptors, delay of isoproterenol induced after depolarisations was shown in isolated guinea pig ventricular myocytes.

Ranolazine lengthened epicardial monophasic APD but did not increase apex-base dispersion of APD nor induce ventricular arrhythmias in isolated female rabbit hearts. Consistent with antiarrhythmic activity was the finding that ranolazine prevented pause dependent ventricular arrhythmias induced by positive controls, at concentrations that inhibit IKr and late INa in canine ventricular myocytes. However, the specificity of these effects was not evaluated with other QT prolonging drugs that inhibit multiple ionic currents, for example terfenadine and cisapride.

The sponsor argued that ranolazine does not have pro-arrhythmic activity since it does not induce early after depolarisations, or increase M cell APD90 or TDR in isolated canine cardiac wedge preparations. Ranolazine was additionally negative for in vitro pro-arrhythmic effects in this preparation, since torsades like arrhythmias did not occur spontaneously and could not be elicited with a single extra stimulus in its presence. The sponsor noted that epicardial stimulation was utilised for these studies, since stimulation at this site was necessary to capture the pro-arrhythmic activity of cisapride, presumably due to increased TDR at baseline. One study showed ranolazine lengthened the M cell APD and increased TDR, but only in the presence of (low) 2 mM potassium. The difference in

[11] IKr = Rapid delayed rectifier potassium current

findings may be explained by the known enhancement of drug induced IKr inhibition by hypokalaemia.

It is noted in the PI that a number of electrophysiological effects, including dose and plasma concentration related increases in the QT interval corrected for heart rate (QTc) interval, reductions in T wave amplitude, and, in some cases, notched T waves, have been observed in patients treated with Ranexa. The PI noted that "*these effects are believed to be caused by ranolazine and not by its metabolites*", but there were no nonclinical data to support this statement and the veracity of the statement is dependent on clinical data.

Central nervous system effects

Central nervous system (CNS) safety pharmacology investigations were extensive. Convulsions featured prominently in the deaths of animals in the acute and repeat dose toxicity studies. In the CNS safety pharmacology studies ranolazine tended to increase the lethality of seizures at lower doses (10 to 30 mg/kg), while higher doses caused signs of sedation (> 80 mg/kg) and decreased the incidence of induced seizures to a point where they were extinguished (100 mg/kg).

In mice given ≥ 100 mg/kg ranolazine, the gross behaviour test resulted in evidence of CNS depressant activity, and sedation (and neurological deficit at lower doses) was indicated in the various tests of for neurological and skeletal muscle coordination and function. This was consistent with the clinical signs, especially subdued behaviour, which was observed at high doses in the acute and repeat dose toxicity studies in all species investigated. Prolonged sleeping time was seen at the HD of 50 mg/kg in the hexobarbital sleep study (a dose not associated with sedation in these studies). Sedation was noted in the hot plate analgesia test, but analgesia appeared to be unaffected.

Mydriasis was reported at 100 mg/kg in addition to decreased activity, ataxia, decreased grip strength, loss of orientation, loss of righting reflex and decreased temperature and muscle tone. Neurologic deficits were elicited at every dose tested (with no observable effect level (NOEL) identified) with an ED50 of 64 mg/kg.

Other systems

Studies on respiratory and gastrointestinal safety pharmacology studies were poorly designed (no controls) and/or poorly reported such that firm conclusions could not be drawn. Renal safety pharmacology studies were not conducted.

The safety pharmacology findings were consistent with those seen in the toxicity studies, and showed low animal:human exposure margins for CNS toxicity (convulsions and increased mortality in rats and dogs at plasma concentrations approximately 3 fold higher [approximately 20 μM] than the proposed maximum recommended clinical dose). While the Risk Management Plan (RMP) acknowledges this low margin it also notes that similar effects have not been observed clinically at supra therapeutic doses of ranolazine, and that the nonclinical data cannot be used to predict clinical experience in this regard. Therefore, occurrence of dizziness will be subject to routine pharmacovigilance.

Pharmacokinetics

Ranolazine was rapidly and extensively absorbed following oral administration in both laboratory species and humans with Time to reach the maximum plasma concentration (T_{max}) occurring within 1 hour post-dose at doses ≤ 100 mg/kg in rodents and ≤ 25 mg/kg in dogs. At higher doses, T_{max} values increased, which may indicate a prolonged absorption phase and/or slower distribution and elimination. In humans, a later T_{max} was observed following administration of the proposed commercial PR formulation. The oral bioavailability of ranolazine was 63 to 71% in rats, 28 to 65% in dogs and 35 to 50% in humans.

The exposure to ranolazine following oral administration tended to increase more than dose proportionally in rats, dogs and humans. The effect was most noticeable at the lower doses in animals. In rats, exposure to ranolazine was generally higher in females than in males. This may be due to differential expression of some cytochrome P450 (CYP450) isozymes in male and female rats, but this was not clear from the data provided in the submission. There were no clear effects of gender in dogs. There were indications that exposure to ranolazine increased over time in some studies, but the findings were not consistent, and a clear attribution to age could not be established. No age related effects on the pharmacokinetics of ranolazine were noted in the "Summary of Clinical Pharmacology, Population Pharmacokinetics", following population pharmacokinetic evaluation of data from patients and healthy volunteers.

Total radioactivity was widely distributed to tissues and organs in rats following oral administration of [^{14}C]-ranolazine and was eliminated at the same rate from most tissues as from plasma. Binding of total radioactivity to ocular melanin was observed following a single oral administration of [^{14}C]-ranolazine, reversible with a half-life of approximately 8 to 23 days.

Moderate plasma protein binding of [^{14}C]-ranolazine occurred, and this was similar in all species. In humans, the binding of [^{14}C]-ranolazine to human α-1 acid glycoprotein was saturated at higher concentrations, but there was no evidence to suggest that any alteration in plasma protein binding in vivo would result in clinically significant changes in the free fraction. The binding of the metabolites RS-88390, CVT-4786 and RS-89289 to human plasma was slightly higher and of RS-94287 was much lower, than that of ranolazine.

Ranolazine was extensively metabolised in all animal species investigated as well as in humans, therefore metabolic clearance was the predominant mechanism of elimination of ranolazine in all species. Metabolism resulted in approximately 14 primary metabolites, many of which, following further Phase 1 and Phase 2 metabolism, in turn gave rise to numerous secondary metabolites.

All major metabolites found in humans were also found in the species used in toxicology studies (mice, rats, and dogs), although there were quantitative differences: RS-89664 conjugate, a minor Phase 2 metabolite, was detected in human plasma, accounting for 6.4% of the $AUC_{0\text{-}24\,h}$, but was not found in the animal species. However, the corresponding Phase 1 metabolite, RS-89664 was formed following in vitro incubation with mouse and rat (but not dog) liver microsomes at rates comparable with that of human liver microsomes, indicating that this metabolic pathway also was present in the rodent species. The Phase 1 metabolism of ranolazine in vitro in liver microsomes was qualitatively consistent with those formed in vivo in the respective species.

Ranolazine was metabolised in human liver microsomes mainly by CYP3A4 to form RS-94287, RS-88390, RS-88681, RS-89961, RS-88640, RS-88772 and its positional isomers.

CYP2D6 resulted in the formation of RS-88390, RS-88640 (also a substrates of CYP3A4), and RS-89961. Ranolazine was not metabolised to any significant extent by CYP2C9, CYP2C19, CYP2E1, CYP1A2, and CYP2B6.

In human liver microsomes, ranolazine and two of its predominant metabolites, RS-94287 and RS-88390 (at up to 100 μM), did not significantly inhibit the metabolism of the marker substrates for CYP1A2, 2C8, 2C9, 2C19, and 2E1. Ranolazine and RS-88390 showed weak competitive inhibition towards CYP3A4. Another major metabolite (RS-94287) had no inhibitory effect on any of the CYP3A4 and CYP2D6-mediated reactions.

Overall, the results indicate that ranolazine has potential for CYP3A4 and CYP2D6 based drug interaction when given concomitantly with drugs also metabolised by these two enzymes.

A potential metabolic pathway for ranolazine and a number of its metabolites is amide bond hydrolysis to form 2,6-dimethylaniline (DMA), a putative nasal mucosa carcinogen in rats, and (in the case of ranolazine) the carboxylic acid RS-91347. RS-91347 was detected in vivo in mice and rats but not in humans, but was detected in the microsomal incubates following incubation with human liver microsomes. In vitro and in vivo studies provided no evidence that DMA is a metabolite of ranolazine in humans.

Excretion studies conducted using oral [^{14}C]-ranolazine in mouse, rat, hamster, dog and humans showed that excretion of total radioactivity was similar in each animal species, was generally independent of dose, and most of the administered dose (60 to 70%) was excreted in the first 24 hour after dosing. Excretion was slower in the dog than in the other animal species, especially at higher doses.

In humans, a greater proportion of the dose was eliminated via urine than in animal species following a single oral administration of [^{14}C]-ranolazine. This suggests that there is a reduction in biliary elimination and higher bioavailability in humans. There was no evidence to suggest any significant accumulation of ranolazine or its metabolites in animal species and humans. The rates and routes of excretion in mice were unaffected following repeated oral administration, and were similar in rats and dogs following IV administration.

The high proportion of the administered dose recovered in faeces indicates that ranolazine was eliminated into the gastrointestinal tract from the systemic circulation. Approximately 60% of the administered dose was excreted in bile collected from bile duct cannulated dogs following oral administration of [^{14}C]-ranolazine. There was a reduction in the excretion of total radioactivity in faeces, as expected, and also in urine. Assuming significant reabsorption occurred in the gastrointestinal (GI) tract, there is the possibility that enterohepatic recirculation may occur in dogs, but this was not specifically investigated.

The excretion of total radioactivity in the milk of lactating animals was not investigated. This issue is addressed in the PI.

Ranolazine was also shown to be a substrate for P-glycoprotein in canine MDCK-MDR1[12] cells in vitro. Ranolazine also inhibited the P-glycoprotein transport of various HMG-CoA[13] reductase inhibitors including simvastatin, lovastatin, and atorvastatin ($IC_{50} \geq 40$ μM). Therefore P-glycoprotein counter transport may affect the oral bioavailability of ranolazine and there is potential for interactions with other P-glycoprotein substrates.

Relative exposure

The proposed maximum clinical dose is 1,000 mg BD per day. This dose is equivalent to 40 mg/kg/day for a 50 kg person. Clinical Study CVT 3015 was a three-way cross over study in which 1,000 mg doses of PR ranolazine (the product proposed for registration) was administered to 20 healthy volunteers with the following dosing regimen: Single dose on Day 1, BD dosing on Days 2 to 5 and a single dose on Day 6. Steady state was achieved within the dosing period with all but 4 of the pharmacokinetic profiles. Pharmacokinetic parameters measured on Day 6 were $AUC_{0\text{-}12\,h}$ (32.9 μg.h/mL), C_{max} (3.83 μg/mL) and terminal elimination half-life (t½) (6.8 h). These data (AUC multiplied by 2 to account for the BD dosing regimen) were used to calculate the animal/human exposure ratios in Table 6. The resulting ratios are lower than those calculated by the sponsor, because these

[12] MDCK = Madin-Darby canine kidney cells MDR = Multi-drug resistance
[13] HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A

were based on 70 kg body weight, and AUC values were not multiplied by 2 to account for the BD dosing. On Day 5 the geometric mean $AUC_{0\text{-}12\,h}$ was 30.2 µg.h/mL, which was 2.7 fold the AUC value for the 500 mg dose under the same dosing regimen, indicating an over proportional increase in AUC with dose.

In the repeat dose toxicity studies, toxicokinetic data were only provided from studies of duration ≥ 26 weeks in rats and dogs, and up to 11 weeks in hamsters. These data are tabulated below. Therefore, where applicable, exposure comparisons for the higher doses used in the shorter duration studies were extrapolated from toxicokinetic data in these longer duration studies.

For the carcinogenicity studies in rats and mice, no toxicokinetic AUC data were provided, and therefore exposure ratios were calculated on a body surface area (mg/m^2) basis (by multiplying the mg/kg doses in mice, rats and humans by 3, 6 and 33.4, respectively). Toxicokinetic data were not provided from pregnant animals, and therefore the exposure ratios in the reproductive toxicity studies were also calculated on a body surface area basis (by multiplying the mg/kg value by 15 for rabbit, and 6 for rat as indicated above).

Table 6: Exposure comparison for pivotal animal studies

Species	Study duration (weeks)	Doses (mg/kg/day)	C_{max} (µg/mL)		$AUC_{0\text{-}24\,h}$ (µg.h/mL)		Exposure ratio*			
							C_{max}		$AUC_{0\text{-}24\,h}$	
			M	F	M	F	M	F	M	F
Rat	26	2, 5, 50, 150	0.1, 0.7, 5.2, 19	0.4, 1.7, 7.0, 16	0.2, 1.3, 23, 117	1, 5, 50, 167	0.04, 0.2, 1.3, 5.0	0.1, 0.4, 1.8, 4.1	0.003, 0.02, 0.3, 1.8	0.02, 0.08, 0.8, 2.5
	26^	2, 20, 50, 200	0.1, 3.3, 8.9, 18	0.3, 5.7, 8.9, 27	0.4, 7.7, 28, 132	0.8, 18, 65, 232	0.03, 0.9, 2.3, 4.6	0.09, 1.5, 2.3, 7.0	0.006, 0.1, 0.4, 2.0	0.01, 0.3, 1.0, 3.5
Dog	26	5, 25, 60	0.7, 3.7, 9.2	0.7, 4.0, 9.9	1.7, 10, 30	1.4, 7.4, 28	0.2, 1.0, 2.4	0.2, 1.0, 2.6	0.03, 0.2, 0.4	0.02, 0.1, 0.4
	52	25, 60	2.1, 6.5	3.5, 13	8.2, 30	8.9, 40	0.6, 1.7	0.9, 3.3	0.1, 0.4	0.1, 0.6

^12 month study, but data are from the 6 month time point; *Plasma C_{max} and AUC animal:human exposure ratios based on (steady state) C_{max} = 3.83 µg/mL $AUC_{0\text{-}12h}$ x 2 = 65.8 µg.h/mL at 1000 mg BD (the maximum recommended clinical dose) (Study no. CVT 3015; Module 2.72, page 20).

In the toxicokinetic studies, the maximal systemic exposures to ranolazine in rats ($AUC_{0\text{-}24h}$) and dogs ($AUC_{0\text{–}8h}$), were approximately 3.5 and 0.6 times, respectively, the maximum systemic exposure in humans ($AUC_{0\text{–}12h}$ x 2) at steady state following administration of the maximum proposed therapeutic dose. The maximal plasma concentration observed in rats, and dogs was approximately 7 and 3 times, respectively, the C_{max} observed in humans following oral administration of the maximum proposed therapeutic dose, and 1.4 times in mice after 24 months dosing (not shown in the table).

It is noted that most of the unconjugated metabolites also had significant late INa blocking ability relative to ranolazine. Therefore, calculations of the animal/human exposure ratios from rats and dogs (species used in the pivotal toxicology studies) were made using exposure ($AUC_{0\text{-}24\,h}$) data for all the metabolites which resulted in an $AUC_{0\text{-}24\,h}$ > 8% of the ranolazine parent following a single dose of ranolazine in humans. However, since the exposure ratios were comparable using this method, the exposure calculations in Table 6 above were based on data with ranolazine alone. Of these individual metabolites, one (CVT-2514 = RS-88390) resulted in lower exposure ratios than the parent in both species. This metabolite had relatively high exposure as well as activity in humans in vitro (72%).

Overall, the animal:human exposure margins derived from the nonclinical studies were low.

Toxicology

General toxicity

The toxicity of ranolazine was investigated in a series of oral and IV single and repeat dose studies up to 12 months duration in rats and dogs. Additional oral studies were conducted in mice and hamsters. The cardiovascular toxicity of ranolazine has been discussed under "safety pharmacology" above.

There were no treatment related deaths in the pivotal repeat dose toxicity studies in dogs but mortality was observed in rats at the highest doses in most studies due to CNS toxicity.

Generally the findings comprised organ weight variations as well as haematological and/or clinical chemistry changes in rats and/or in dogs. The weights of heart, liver, kidney, spleen, adrenal gland, brain, pituitary gland and/or uterus were affected in some studies. With the exception of the adrenal gland, there were no histopathologic changes in any of these organs in either species in any study. The rat adrenal changes are discussed in detail below.

There was a tendency towards small (but statistically significant at the highest doses) reductions in erythrocytic parameters in both species, as well as increases in the incidence of target cells in rats. This may reflect a mild effect of ranolazine on the peripheral blood, since there was no evidence of bone marrow toxicity, but no further investigations to address this were conducted. Consistent with the erythrocytic findings, according to the "clinical overview", small decreases in red blood cell counts and haematocrit were also reported in clinical studies. Increased spleen weights (in female rats after 3 and 6 months treatment at ≥ 200 mg/kg/day), and slightly increased platelet numbers (in male rats in the 12 month study) were also seen.

Distribution to the skin was seen in pigmented rats. Irritation at the injection sites were seen in one (IV) study in dogs. The clinical significance of these findings is not clear.

Acute toxicity

Single dose studies in rats and mice indicated a minimum lethal dose for ranolazine dihydrochloride of approximately 250 mg/kg by oral gavage and > 30 mg/kg when given IV. However, there were 3/3 deaths at 300 mg/kg in a mouse PO safety pharmacology study but no deaths at the same dose in a micronucleus study. There was no indication of any gender differences in any study and no evidence for any difference between the enantiomers and the racemate when given by gavage to rats. In range finding repeat dose studies in dogs, deaths occurred following a single oral dose of 150 mg/kg and following a single IV dose of 40 mg/kg. Deaths in all species were associated with neurotoxicity related findings (convulsions, collapse, ataxia, and subdued behaviour). No consistent gross pathology was identified in dead animals.

Adrenal toxicity

Changes were consistently observed in the adrenals of rats, following oral gavage dosing particularly at ≥ 200 mg/kg/day. These findings included (in both sexes) increased adrenal weights (by up to 70%), enlarged adrenals (macroscopically) and vacuolation or foaminess in the zona fasciculata and zona reticulata (under histological examination). Although the findings were most notable at the highest dose, the adrenal changes occasionally, but not consistently, extended to lower doses, and appeared to increase in incidence and severity with increasing dose and duration of treatment. The findings also persisted for 1 month after cessation following 6 months treatment (albeit with lower

severity). There were no adrenal changes in the IV study. Hyperplastic and neoplastic changes were also seen in this organ in the 2 year carcinogenicity study in rats, including an increased incidence of medullary hyperplasia, cortical vacuolation and hypertrophy of the zona fasiculata/zona reticularis at ≥ 50 mg/kg/day, and there were neoplastic findings (addressed under "carcinogenicity" below). Mean adrenal weights were increased in dogs (following oral dosing) by up to 27%. Since these changes were generally not dose related or statistically significant and were not accompanied by histological findings, they were considered of equivocal biological significance.

A number of other in vitro and in vivo investigations were conducted in rats, which were designed to specifically investigate the adrenal findings. A 1 month study concluded that the adrenal changes had no influence on the ability to respond to stress in rats. In another study, electron microscopy showed enhanced cellular activity at 300 mg/kg/day and a marked increase in the number and size of intracytoplasmic vesicles, with evidence of fusion between the vesicles and intra-mitochondrial cavities. Mitochondria were often enlarged and increased numbers of lysosomes were present. The mitochondrial changes were consistent with an enhancement of normal secretory activity. There were no degenerative changes.

Inhibition of adrenal steroidogenesis was observed in vitro but only at 100 μM (approximately 43 μg/mL). This was greater than the concentrations achieved in pivotal repeat dose toxicology studies or anticipated in clinical use.

From the evidence provided it is possible that the adrenal changes seen in rats (that is, enlargement, increased vacuolation and cytoplasmic foaminess of the zona fasciculata) were species-specific, and did not appear to result in effects on adreno cortical function. The findings in dogs were limited to increased adrenal weights. According to the clinical overview, endocrine function (adrenal and thyroid) was not affected by long term exposure to ranolazine PR in humans. Therefore, unless there were indications of effect on cortisol levels (performed pre and post adrenocorticotrophic hormone (ACTH) stimulation) or in plasma cholesterol in clinical studies, the rat adrenal changes are unlikely to be of clinical significance.

Thymic toxicity

Cystic hyperplasia of the thymus and thymic cysts were seen in female rats at 200 mg/kg/day in the 12 month study and cysts of the thymus were also seen at 60 mg/kg/day in the 6 month study in dogs (but not in the 12 month study in dogs, with the same doses). The clinical significance (if any) of these findings was not clear.

Hepatic toxicity

Liver fat was specifically assayed in many of the nonclinical studies (using oil-red-O). The studies showed that minor hepatic changes in rats (increased liver weights, cytoplasmic pigment) were consistent with increased plasma cholesterol (seen in rats and hamsters, and in the 3 month study in dogs) and therefore were considered probably secondary to the adrenal changes.

Renal toxicity

Urinalysis of rats revealed increased osmolality of the urine accompanied by increased abnormal components in the microscopy of the spun deposit, sometimes accompanied by increased protein output, in all the pivotal oral studies (3 to 12 months duration) in rats. There was also a tendency towards increased kidney weights in these studies. Generally there were no histopathologic changes in the kidney, but in the 6 month study, there was an increased incidence of pyelitis. In addition, pyelonephritis was seen in 2 animals given 200 mg/kg/day that died during the study, but in no other animals.

Serum chemistry indicated some disturbance of proteins in rats, particularly reduced albumin concentrations. Serum creatinine was slightly but statistically significantly

increased at 200 mg/kg/day in male rats in the 12 month study, and serum urea was increased in male dogs after 6 months treatment at 60 mg/kg/day, but this finding was not statistically significant, and was not seen at the same dose after 12 months treatment. These findings collectively indicated some potential for general kidney toxicity, although the findings were mainly restricted to a single species (rats). According to the clinical overview, the most likely explanation for an increased plasma creatinine that was seen in clinical trials was inhibition of tubular secretion of creatinine by ranolazine. No treatment related clinically meaningful urinary abnormalities were noted during either short- or long-term exposure to ranolazine in clinical studies.

Neurotoxicity

Central nervous system toxicity was addressed in a number of studies described under "safety pharmacology". The limiting toxicity in many of the studies was severe clinical signs including ataxia, prostration, convulsions or other uncontrolled behaviours in mice, rats, dogs and hamsters. Other signs included emesis, salivation, subdued behaviour and/or trembling. These were often accompanied by various ocular findings including mydriasis, ptosis, watery, glazed or half-closed eyes and conjunctival congestion.

While there was evidence of significant distribution of radioactivity to the eyes in pigmented rats following treatment with radiolabelled ranolazine, the findings listed above were not accompanied by ophthalmoscopic findings.

Generally the signs were transient and confined to the period immediately after dosing, but were clearly treatment related. No direct effects were seen on the brain (including organ weights or histopathology), and distribution to the brain was minimal.

Respiratory effects

Respiratory changes were seen in some studies in rats and included foamy macrophages. In the nonclinical overview it was suggested that such findings may have been a consequence of aspiration of either the test formulation or the ingesta during convulsions seen after dosing and is therefore unlikely to represent any direct lung toxicity due to ranolazine. However, this was not specifically investigated and was therefore not conclusively established.

Genotoxicity and carcinogenicity

Genetic toxicology was investigated in an extensive series of in vitro mutagenicity studies in bacterial and mammalian cells, all of which were negative. An in vitro clastogenicity study gave a positive result at high exposures in the presence of an S9 metabolizing system when cells were harvested at 10 hours and this was confirmed in a repeat investigation. A harvest at 20 hours at a higher or equivalent concentration was negative.

In vivo micronucleus tests with ranolazine in both mice and rats were negative, at doses up to 300 and 250 mg/kg, respectively (approximately 8 (extrapolated) and 3 fold the C_{max} at the maximum recommended clinical dose, respectively). In addition, ranolazine did not induce DNA damage in the liver of rats in the in vivo Comet assay at up to 250 mg/kg. It is noted that there is no ICH guideline that refers to the Comet assay, but the assay was conducted (in 2007) in accordance with the recommendations of the IEGTP workshop (2004).[14] The weight of evidence from the in vitro and in vivo studies indicated that neither ranolazine, nor any metabolites produced via metabolic biotransformation in the in vivo studies, were genotoxic.

Carcinogenicity studies were conducted in mice and in rats. Exposure to ranolazine in the mouse study was low and there was no evidence of any toxicity at the highest dose

[14] Hartmann A, et al (2004). Use of the alkaline in vivo Comet assay for mechanistic genotoxicity investigations. *Mutagenesis* 2004; 19: 51-50

investigated, 50 mg/kg/day (150 mg/m^2/day or 0.2 fold the maximum recommended dose on a body surface area basis). Increased mortality in the rat study forced premature termination of this investigation after 21 months of treatment. While the duration of the study was considered sufficient for carcinogenicity assessment, it does suggest that a conservative interpretation of the data is warranted.

There was no evidence for significant trends in organ specific tumours in the mouse carcinogenicity study.

In female rats, the incidences of two types of benign adrenal tumours (phaeochromocytoma and cortical adenoma), were reported by the sponsor to be slightly but statistically significantly increased at 150 mg/kg/day (0.7 fold the maximum recommended dose on a body surface area basis). FDA analysis of the same data (NDA 21-526) suggested p-values that did not reach significance by their standards. Tumour incidences at 150 mg/kg/day appeared to be equivalent to, or slightly greater than, the historical control data provided (but it is noted that all the findings of these rare tumour types were restricted to a single historical control study in both cases). As noted under "general toxicity", there was also a dose related increase in the incidence of medullary hyperplasia (potentially a precursor for phaeochromocytoma), cortical vacuolation and hypertrophy of the zona fasciculate/ zona reticularis. Overall, the adrenal findings are considered to be of equivocal toxicological significance in humans as there are indications (discussed under "adrenal toxicity" above) that rodents are more susceptible to adrenal toxicity.

The incidence of thyroid follicular adenoma, another relatively common tumour type in rats, was statistically significantly increased in male rats at 150 mg/kg/day (0.7 fold the exposure at the maximum recommended clinical dose on a body surface area basis), and this appeared to be accompanied by a small increase in hyperplasia at this dose. The incidence of neoplastic findings (but not the hyperplasia) at this dose was also greater than seen in historical controls. However, there were no pre-neoplastic lesions in the (chronic) repeat dose toxicity studies involving up to 1 year of treatment at higher doses. The concentration of ranolazine-derived radioactivity in the thyroid appeared to be consistently greater than in plasma or whole blood over 120 hours after oral administration in rats. Overall, the finding was considered to be of equivocal toxicological significance.

The origin of the subcutaneous tumours, although not common in rats, was not determined. Distribution of ranolazine derived radioactivity was relatively high to the pigmented skin in rats (but low in albino rats, in which the carcinogenicity studies were conducted).

In a published study,[15] daily treatment of APC(min/+) mice[16] (males only) with intra peritoneal (IP) ranolazine dihydrochloride (up to 60 mg/kg/day) for 30 days resulted in a statistically significant increase in the number of intestinal neoplasms (by about 70%). This was accompanied by an increase in average tumour diameter that was not statistically significant. A trend towards higher levels of dysplasia was seen in the adenomas, and the distribution of carcinomas was shifted towards greater invasiveness, but the statistical significance of these findings was not stated.

[15] Suckow MA et al, 2004 The anti-ischemia agent ranolazine promoted the development of intestinal tumors in APC (Min/+) mice. *Cancer Letters* 2004; 209: 165-169.

[16] The Apc gene is the homolog of human APC (adenomatous polyposis coli) gene, and involves a nonsense mutation in codon 850 of the murine Apc gene. Heterozygous Apc(Multiple Intestinal Neoplasia (Min)/+) mice develop numerous intestinal tumours (adenomas) mainly in the upper gastrointestinal tract. The adenomas grow to a detectable size in one to three months. These mice are used eg as a nonclinical model for Familial Adenomatous Polyposis. For further information see eg http://jaxmice.jax.org/jaxnotes/archive/455a.html

There is limited experience with the use of this model in tumour promotion, and it has not been validated for the purpose of general tumour promotion or carcinogenicity evaluation. The sponsor also questioned the purity of the test material used in the study. It is noted that the spontaneous background incidence reported by another group exceeded the tumour incidence observed in APC(min/+) mice given the high dose of ranolazine (60 mg/kg/day).[15]

Despite deficiencies in the study, the potential for tumour promotion by ranolazine at least in the intestine cannot be ruled out from the study results. In fact, according to the US FDA report, both the Pharmacology/Toxicology Coordinating Committee and an outside consultant from the National Toxicology Program have given their opinions that the safety issue raised cannot be dismissed out of hand and that further laboratory investigation is warranted.

Overall, the rat carcinogenicity studies indicated slight but statistically significant and greater than historical control range increases in the incidence of some tumours, which in some cases were accompanied by slight increases in relevant hyperplasia. On a weight of evidence basis ranolazine was not considered genotoxic and does not appear to have primary carcinogenic potential, but it cannot be ruled out that it may have tumour promotion potential. This should be noted in the PI.

Reproductive toxicity

A fertility study was conducted in which 20 males were mated with 40 females per mating cohort, with both males and females treated with 0, 5, 40 or 300 mg/kg ranolazine (for 80 + and 14 days, respectively). A statistically significant reduction in pregnant females (approximately 30% compared with controls), reflecting a reduction in male and/or female fertility, was associated with atrophic changes in the testes and epididymides of four rats treated at 300 mg/kg/day (approximately1.3 fold the maximum recommended dose on a body surface area basis), indicating effects on male fertility. Two further matings were conducted with the same males, but with untreated females, each of which indicated approximately 30% lower male fertility (compared with controls, where fertility was 100%) after 133 days of treatment at 300 mg/kg/day and after 156 days treatment at that dose followed by a 32 day recovery period. Since the males were only sacrificed after the study had been completed, and since the decrease in the fertility rate was consistently 30%, it is possible that the same animals that were already affected at 80 days were also responsible for the reduced fertility at the latter time points that is no recovery had occurred. These data indicated that ranolazine had the potential to impair fertility in males following 300 mg/kg/day for 80 days or longer. This finding should be noted in the "effects on fertility" statement in the PI.

Atrophic changes were seen in testes of rats treated for 6 months with 5 and 200 mg/kg/day ranolazine (intermediate dose animals were not examined in the study), but not in the testes and epididymides of rats treated for 12 months or in male dogs treated for 3, 6, or 12 months. There were no atrophic changes in the testes and epididymides of male rats at 500 mg/kg/day in a 3 month toxicity study (treatment duration equivalent to that of the male fertility study). Spermatological investigations were not conducted in any of the submitted studies, including the fertility study. The sponsor argued (in the "toxicology written summary"), that the absence of any uniform atrophic histologic changes in the testes and epididymides in chronic toxicity studies in rats and dogs ruled out any direct or indirect effect, via the gonadotropin axis, and therefore, the atrophic changes and consequent reduction in male fertility were a chance finding that could not be ascribed to treatment with ranolazine. However, given the consistency of the male fertility findings, their occurrence at a low exposure margin, and the known large fertility reserve that male rats display, this finding should be noted in the PI.

According to the RMP, there have been no clinical trial or post-marketing reports of decreased male fertility or testicular changes, but the RMP also acknowledged that limited clinical data are available evaluating these effects. The RMP includes a commitment to monitor for evidence of effects on male fertility.

There was an increased incidence of misshapen sternebrae and reduced ossification of pelvic and cranial bones in foetuses of pregnant rats dosed at 400 mg/kg/day (1.8 times the maximum recommended human dose (MRHD) on a surface area basis). Reduced ossification of sternebrae was observed in foetuses of pregnant rabbits dosed at 150 mg/kg/day (1.7 times the MRHD on a surface area basis). These doses in rats and rabbits were associated with maternotoxicity (including increased maternal mortality).

Pregnant Sprague Dawley rats that received up to 200 mg/kg/day ranolazine from gestation day (GD) 15 to post-partum day (PPD) showed no treatment related differences in clinical signs, BW, gestation period, parturition, or litter size. Treatment also had no effect on the clinical condition, growth, or survival of the pups.

There have been no studies in juvenile animals and no investigations of trans-placental transfer or excretion in milk. Ranolazine is not indicated for paediatric use, and it is recommended in the PI that Ranexa should not be given during pregnancy or to nursing mothers.

Pregnancy classification

The sponsor has proposed Category C.[17] This should be amended to Category B3[18] on the basis of the embryofetal findings at very low relative exposure margins (less than 2), irrespective of maternotoxicity.

Use in children

The safety and effectiveness of ranolazine have not been established in paediatric patients. This has been noted in the PI.

Impurities

The impurities associated with ranolazine were either within expected limits or adequately qualified. An exception was the potential hydrolysis product and degradant 2,6 dimethylaniline (DMA), which has been classified by the International Agency for Research on Cancer (IARC) as 'possibly carcinogenic to humans'. Despite being a metabolite in various animal models, DMA did not appear to be a metabolite of ranolazine in humans.

In their response to question raised PM-2009-03753-3-3 by the quality evaluator, the sponsor detailed a method which could detect DMA with an LOD of 20 ppm and noted that levels of DMA remain below this level in tablets stored at 25°C for up to 66 months. However, given that the maximum daily dose of Ranexa will be 2 g per day, the potential maximum daily intake of DMA (based on the LOD) is therefore 40 µg, which is above the threshold of toxicological concern (TTC) for genotoxic impurities (1.5 µg/day). The sponsor was asked to either 1) provide data to demonstrate that DMA is not genotoxic, or 2) add an appropriate limit to the product specifications, or 3) provide data to demonstrate that DMA levels at expiry are consistently below the TTC.

[17] Pregnancy Category C is defined as Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[18] Pregnancy Category B3 is defined as Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The sponsor did not address the specific genotoxicity of DMA in its response. The submitted battery of assays testing ranolazine (potentially containing trace DMA) for genotoxicity was not itself sufficient to qualify DMA for genotoxicity, as the amounts of DMA present in such assays were insufficient to constitute a valid assay. Therefore, if such assays are to be informative, DMA should be tested in isolated form.

In view of the possibility that DMA is genotoxic, and that patients for this indication will potentially be chronically exposed to this impurity, the quality evaluator was advised that exposure to DMA through treatment with ranolazine should be limited to the TTC (1.5 µg/day) corresponding to a level of DMA in the product at shelf life of NMT 0.75 ppm.

Nonclinical summary and conclusions (from submission PM-2009-03573-3-3)

- While many of the nonclinical studies were conducted prior to GLP requirements being applicable, the key toxicity and pharmacokinetics studies were GLP-compliant. Studies were conducted across a suitable range of species using appropriate doses and were generally of adequate duration. Animal:human exposure ratios tended to be low due to dose limiting toxicity.
- The mechanism of action of ranolazine is largely unknown. Pharmacological data suggested that it inhibited the late inward sodium current (INa) with higher potency than flecainide and dofetilide, reduced myocardial [Ca2+]i overload, and had anti-ischaemic efficacy independent of any effects on HR, arterial BP, left ventricular contractility, or systemic vascular resistance. Receptor binding screens showed that ranolazine and its R- and S-enantiomers had moderate affinity for α1-adrenergic receptors, β1-adrenergic receptors, β2-adrenergic receptors, and serotonin (5-HT) 5-HT1A and 5-HT2 receptors, but whether blockade of such receptors contributes to the overall clinical pharmacology profile is unclear.
- Safety pharmacology studies showed that ranolazine caused central sedation and had effects on the hypothalamus pituitary adrenal (HPA) axis in rats. Ranolazine had negative inotropic effects and anti-arrhythmic activity, and did not appear to have torsadogenic potential despite its inhibition of IKs[19] and IKr and its moderate prolongation of QT interval. Few detrimental effects of ranolazine were seen at plasma concentrations within the expected therapeutic range (≤ 10 µM).
- No significant haemodynamic interaction of ranolazine was observed in dogs, with long acting nitrates and the phosphodiesterase-5 inhibitor, sildenafil.
- Ranolazine was rapidly absorbed and was extensively metabolised after oral administration in all species investigated. Bioavailability was similar across all laboratory species and humans. Ranolazine and its metabolites were distributed widely, and there was evidence for reversible melanin binding. One conjugated metabolite was identified in humans at low levels but not in any laboratory species, but the unconjugated metabolite was found in studies with rat, mouse and human liver microsomes. There was no evidence of any interconversion of the R- and S-enantiomers in vivo. Approximately 45% of the total radioactivity was excreted in urine and nearly 55% in the faeces in animals, while in humans, 70% was excreted in the urine. Exposure in humans was generally greater than in animal studies.
- Ranolazine was metabolised mainly by CYP3A and to a lesser extent by CYP2D6. Ranolazine also was a substrate for P-glycoprotein in canine MDCK-MDR1 cells in

[19] IKs = Slow delayed rectifier potassium current

vitro, and inhibited the P-glycoprotein transport of various HMG-CoA reductase inhibitors.

- Toxicity to the central nervous system (CNS) including convulsions, ataxia, prostration, and eventual death was shown with little or no exposure margin in the repeat dose toxicity studies, as well as the safety pharmacology studies. Adrenal gland toxicity was consistently observed in rats and special mechanistic studies showed both acute and chronic effects on the HPA axis. These changes were not of clinical concern as microscopic changes observed in rats were not seen in dogs and there were no apparent effects on adreno-cortical function in either the nonclinical or clinical data. Minor, treatment related effects were also observed in kidney and liver at the highest doses but did not raise any particular concerns.
- In vitro mutagenicity studies in bacterial and mammalian cells were all negative. While some chromosomal aberrations were noted with ranolazine in vitro in CHO cells under certain conditions, ranolazine tested negative in the in vivo micronucleus test and in a Comet assay. Therefore, the overall evidence suggests that ranolazine is not genotoxic.
- The weight of evidence from studies in mice and rats suggests that ranolazine has no primary carcinogenic potential although the highest oral doses were less than the maximum recommended human dose (MRHD) of 2 grams on a surface area basis. A published study reported that ranolazine promoted tumour formation and progression to malignancy when given to transgenic APC (min/+) mice at a dose of 30 mg/kg twice daily.[20] As the clinical significance of this finding is unclear (see Assessment), the potential tumour promoting activity of ranolazine should be noted in the PI (PI).
- In the reproductive toxicity studies, atrophy of the testes and epididymides and reduced fertility was seen in males. At maternotoxic doses, growth retardation was observed but without evidence of fetal malformations. These findings are noted in the PI. Other reproduction changes were seen only at maternally toxic doses and were limited to reduced survival during Days 1 to 4 post-partum, reduced ossification, and delayed development characteristics. None of these suggest any direct effect of treatment on the 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 (1.8 fold and 1.7 fold the maximum recommended dose in humans on a body surface area basis, respectively).
- None of the studies addressed whether ranolazine or its metabolites passes the placenta and/or is secreted into the breast milk of lactating animals. Hence, the statements in the PI need to indicate that ranolazine should not be used during pregnancy or lactation.
- A potential hydrolysis product and degradant of ranolazine is 2,6 dimethylaniline (DMA), which has been shown to be a metabolite in animals but not in humans. Sensitivity limitations of the analytical assay for DMA suggest that the maximum daily intake of DMA could be up to 40 µg/day. Since the genotoxicity of DMA was not addressed in the submitted studies, and because patients for the proposed indication will potentially be chronically exposed to this impurity, the Pharmaceutical Chemistry Evaluation Section has been advised that exposure to DMA through treatment with ranolazine should be limited to the Threshold of Toxicological Concern (1.5 µg/day) corresponding to a level of DMA in the product at shelf life of NMT 0.75 ppm.

[20] Suckow MA et al The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC(Min/+) mice. Cancer Letters 2004; 209: 165-169

Conclusions and recommendations

The nonclinical studies indicated that ranolazine improved heart functional parameters following artificially-induced ischaemia in animal models. Ranolazine (and in some cases, some of its metabolites) also reduced intracellular calcium accumulation and inhibited the late sodium current in preference to the peak sodium current in in vitro models at clinically relevant concentrations.

Findings from safety pharmacology studies (only one of which was GLP-compliant) included negative inotropic cardiovascular effects, but without evidence of histological findings in toxicity studies. CNS effects included convulsions and central sedation and were found to be dose limiting in the toxicology studies. The Risk Management Plan (RMP) noted the low safety margin to these CNS findings, but also maintained that similar effects have not been observed clinically. Dizziness is noted in the RMP, and there is a commitment to monitoring as part of routine pharmacovigilance.

The weight of evidence suggests that ranolazine is not genotoxic and does not have primary carcinogenic potential. However, studies in a specific type of transgenic rat suggested that ranolazine may have some tumour promoting potential. While the clinical relevance of these findings is unclear, they should be noted in the PI in the Carcinogenicity section.

Ranolazine was not teratogenic at the doses employed. Reproductive toxicity findings were restricted to maternotoxic doses and included reduced fertility in males (rat fertility study) and growth retardation without evidence of fetal malformations (rat and rabbit embryofetal development studies). These findings are noted in the PI and it is noted that the RMP contains a commitment to monitoring effects on male fertility.

The maximum daily intake of the potential ranolazine hydrolysis product and degradant 2,6 dimethylaniline (DMA), which is a metabolite in animals but not in humans, is up to 40 µg (based on the analytical assay Limit of Detection). Given that the genotoxicity of DMA was not addressed in the submitted studies and that patients will potentially be chronically exposed to this impurity, exposure to DMA through treatment with ranolazine should be limited to the TTC (1.5 µg/day) corresponding to a level of DMA in the product at shelf life of NMT 0.75 ppm.

There are no objections to the registration of ranolazine on nonclinical grounds subject to the following actions by the sponsor: 1) Implementation of RMP commitments as described above, 2) Amendments made to the PI as described and 3) Satisfactory resolution of the DMA issue noted above.

Nonclinical report for submission PM-2015-00423-1-3

A Menarini Australia Pty. Ltd. has applied to register the new chemical entity ranolazine (Ranexa). Ranolazine is indicated for use in adults as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first line anti–anginal therapies. Ranolazine is formulated as a prolonged release tablet at three strengths (375 mg, 500 mg and 750 mg) and is to be administered at up to 750 mg twice daily (1500 mg/kg/day, PO).

PM-2015-00423-1-3 is a resubmission of a previous application (PM-2009-03573-3-3; see TRIM: R11/314142 and R11/9937). The nonclinical data set is generally the same as that previously provided, with the exception of a new in vitro study concerning the effects on uptake and efflux transporters (Study AD-259-2005). As well, the sponsor provided two toxicological risk assessment reports to justify the presence of 2,6 – dimethyl aniline as a non-specified impurity.

Assessment

As most of the nonclinical data set has been previously evaluated, no further comment is provided on the main pharmacological, pharmacokinetic and toxicological properties of ranolazine.

With regard to the new data, an in vitro study on the effects of ranolazine on uptake and efflux transporters found no inhibitory activity of ranolazine against uptake transporters organic anion transporting polypeptide (OATP) OATP1B1 and OATP1B3 (IC_{50} > 100 μM), or the efflux transporter breast cancer resistance protein (BCRP) (IC_{50} > 6,000 μM). However, ranolazine exhibited inhibitory activity against P-glycoprotein (P-gp) (IC_{50} approximately 15 μM). Relative to conditions of use, this interaction is likely to be clinically relevant. The PI notes a steady state C_{max} of 1,770 ng/mL (or approximately 4 μM) following a dose of 500 mg twice daily (noting that the MRHD is 750 mg twice daily). Clinical evidence of this drug interaction (approximately 1.5 fold increase in plasma digoxin levels when co-administered with ranolazine) is also described in the Interactions section of the PI. There are no further nonclinical comments on this issue.

In the previous application, an outstanding issue concerned the presence of the unspecified process and degradation impurity 2,6-dimethylaniline (DMA also known as 2,6-xylidine) in drug product Ranexa. DMA is a known mutagen and the IARC categorises it as a Class 1 carcinogen (mutagenic impurity with positive carcinogenicity data). In the resubmission the sponsor once again did not nominate a specification limit for DMA but referred to an updated analytical method [Study RA-305-13 – validated LC-MS/MS, detects DMA at a limit of quantification of up to 0.2 ppm, which according to 3.2.P.2.2 corresponded to 0.15 μg/tablet] and provided batch analyses results showing negligible levels of DMA in ranolazine API, while at 24 months levels ranged between 1.23 to 2.43 ppm/tablet or 0.92 to 1.83 μg/tablet for the 750 mg dosage.

Table 7: Amounts of DMA found in Ranolazine PR film-coated tablets stored in ICH conditions

Batch	Strength (mg)	Manufacturing Date	API manuf	Analysis Date and Storage Conditions	DMA content	
					ppm/tablet	µg/tablet
28038 28054 28055	375	Oct 12 Dec 12 Dec 12	Huahai	analysed after 18 months stored in ICH conditions at 25°C/60% RH	1.09 0.94 1.42	0.41 0.35 0.53
				analysed after 24 months stored in ICH conditions at 25°C/60% RH	1.80 1.62 1.42	0.67 1.11 0.53
28032 28048 28049	500	Oct 12 Nov 12 - Dec 12 Nov 12 - Dec 12	Huahai	analysed after 18 months stored in ICH conditions at 25°C/60% RH	1.19 1.39 0.88	0.59 0.69 0.44
				analysed after 24 months stored in ICH conditions at 25°C/60% RH	1.84 1.67 1.25	0.92 0.83 0.63
28009 28010 28011	750	Oct 12 – Nov 12 Dec 12 – Jan 13 Dec 12 – Jan 13	Huahai	analysed after 18 months stored in ICH conditions at 25°C/60% RH	1.50 1.03 0.94	1.12 0.77 0.71
				analysed after 24 months stored in ICH conditions at 25°C/60% RH	1.96 1.43 1.23	1.47 1.07 0.92
28017 28018 28019	375	May 12 – Jun 12 May 12 – Jun 12 May 12 – Jun 12	FIS	analysed after 24 months stored in ICH conditions at 25°C/60% RH	2.56 2.51 3.18	0.96 0.94 1.19
28014 28015, 28016	500	May 12 – Jun 12 May 12 – Jun 12 July 2012	FIS	analysed after 24 months stored in ICH conditions at 25°C/60% RH	2.91 1.60 2.67	1.46 0.80 1.33
28006 28007 28008	750	June 2012 June 2012 July 2012	FIS	analysed after 24 months stored in ICH conditions at 25°C/60% RH	1.75 1.92 2.43	1.31 1.44 1.83

The sponsor also commissioned two nonclinical risk assessments on DMA relative to potential exposure from ranolazine under the conditions of use. Both assessors referred to methodologies advocated in the ICH guideline.[21] The updated guideline permits the use of compound-specific assessments (compared with. TTC-based acceptable intake of 1.5 µg/day) when sufficient carcinogenicity data exists, such that a compound-specific acceptable intake can be extrapolated from measures of carcinogenic potency. Information on the carcinogenicity of DMA is available from a 2 year dietary study in rats (NTP, 1990) and is the only source of data on carcinogenic potency.

The first nonclinical assessor referred to a follow-up report to the NTP report where carcinogenic potential (TD50) was set at 20.4 mg/kg. By linear extrapolation the acceptable lifetime daily intake was calculated as 0.41 µg/kg/day (24.5 µg/day for 60 kg adult or 20.4 µg/day for 50 kg adult). The amount of DMA detected in 750 mg ranolazine tablets after 24 months storage (1.6 µg/tablet or 3.2 µg/day based on average batch values outlined above in Table 7) were at least 6.4 fold lower than the extrapolated acceptable lifetime daily intake of 20.4 µg/day (for 50 kg adult at the MRHD). The assessor indicated that this was an acceptable safety factor but recommended that the shelf life of Ranexa be no more than 24 months to ensure ranolazine degradation was minimal.

The second nonclinical assessor evaluated risk assessments conducted by other regulatory bodies where acceptable daily levels of DMA ranged between 20.4 µg/day to 110 µg/day (for 50 kg adult). The most conservative approach gave acceptable daily levels of 29 µg/day (20.4 µg/day for 50 kg adult) and was the same as that outlined by the first

[21] ICH M7 – Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (Step 4).

assessor. The second assessor concluded that there were sufficient multiples between the levels of DMA detected in batches at shelf life and the compound-specific acceptable daily limit of 29 µg/day (or 20.4 µg/day for 50 kg) such that it posed a negligible risk of carcinogenesis and did not require additional controls. It is noted that some of the supporting references used in the risk assessments were not found in the submission.

The inclusion of an updated analytical method with a lower limit of quantification provides some assurance that levels of DMA at expiry are at sufficiently low multiples of the acceptable intake level range. It is noted in the drug product specifications that the sponsor nominated acceptance criteria for unspecified degradation impurities at NMT 0.1%, equating to 1.5 mg/day for any degradant at MRHD, and could potentially include DMA. This is unacceptably high (and well above the acceptable daily intake level range) thus the sponsor should explicitly exclude DMA from this limit. Although the sponsor did not conduct any further investigations on DMA, the commissioned risk assessments provided adequate assurances that potential exposure to DMA is negligible when used at release and will be unlikely to pose a significant risk of carcinogenicity when used at release levels. However, as it is clear that DMA levels increase over time and the specifications are somewhat ambiguous on whether non-specified degradation impurities include DMA, the sponsor should ensure that the shelf life for Ranexa is kept to 24 months or lower to minimise the potential exposure to DMA through degradation.

The nonclinical evaluator also made comments regarding the PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor states that ranolazine exerts its anti-anginal and anti-ischemic effects by inhibition of the late sodium current (late INa) in cardiac cells. This reduces intracellular sodium accumulation and consequently decreases intracellular Ca^{2+} overload. Therefore ranolazine acts to reduce these intracellular ionic imbalances during ischemia. Reduction in cellular Ca^{2+} overload is expected to reduce myocardial stiffness, oxygen consumption, and adenosine triphosphate (ATP) utilisation, and to improve blood flow to the microvasculature. It is claimed that the effects of ranolazine do not depend upon reductions in heart rate (HR), or blood pressure (BP), or upon vasodilation.

The rationale given in the Clinical Overview for a new anti-anginal agent was:

"Despite additional drugs and/or revascularization many patients remain symptomatic and/or have poor exercise performance. Thus, there are a substantial number of patients for whom the currently available agents are sub-optimal in so far as they are contraindicated or do not alleviate symptoms or produce unacceptable side effects. Ranolazine is an anti-anginal drug that offers a treatment option with a novel non-hemodynamic mechanism of action".

Australian regulatory history

The clinical development programme for ranolazine commenced in 1985 sponsored by [information redacted] with initial studies of intravenous (IV) and immediate release (IR)

formulations. In order to maintain an effective plasma concentration, an extended release (ER) formulation was developed. It appears the development of ranolazine was ceased by [information redacted] in about 1994. In 1996, [information redacted] acquired the rights to ranolazine and continued development of ranolazine ER in chronic angina pectoris. [Information redacted] was then acquired by [information redacted]. The sponsor stated that due to changes in commercial agreement the product license was transferred to A Menarini International Operations Luxembourg SA (date of transfer was not stated). Gilead is the marketing authorisation holder in the US and Israel and Menarini is responsible for Europe and other non-European countries.

In 2009, Gilead Sciences submitted an application to register ranolazine (PM-2009-03573-3-3). The application sought the registration of 500 mg and 1,000 mg extended release tablets and the proposed indication was for the treatment of chronic angina. The clinical evaluation report found that the benefit-risk balance is negative for the use of ranolazine as first line, monotherapy treatment and its use should be restricted to add on therapy. In addition, it was recommended that the 750 mg BD dose be made available and questioned the safety of the 1,000 mg dose in populations at risk of increased exposure. This application was subsequently withdrawn by Gilead. The sponsor stated the reason for withdrawal was "Unable to provide a full and complete response in the timeframe required, in relation to the impurity method and method validation".

This dossier is a resubmission which is applying for different ranolazine PR strengths (375, 500 and 750 mg tablets) and a different indication in chronic angina (as add on or second line therapy).

Contents of the clinical dossier

The submission contained the following clinical information, much of which had been previously submitted in the dossier PM-2009-03573-3-3:

The efficacy and safety studies were:

- 15 bioavailability studies (2 new)
- 1 in-vitro in-vivo correlation
- 18 bioanalytical reports (1 new)
- 45 pharmacokinetic (PK) studies (6 new)
- 15 pharmacodynamic (PD) or PK/PD studies (1 new; GS-US-270-0101)
- 1 population PK study (CVT303.019-C)
- 15 controlled clinical studies pertinent to claimed indication (CL 5836, CVT 3031, CVT 3033, CVT 3036, CVT 3037, RAN012, RAN015, RAN020, RAN054, RAN072, RAN080, RAN1490, RAN1514, RAN1789, RAN2240) (all previously submitted)
- 8 uncontrolled clinical studies (7 previously submitted – CVT 3024, CVT3032, CVT 3034, CVT 3114, RAN081, RAN1515, RAN2074; and 1 new; CVT 3041)
- 3 reports using pooled data (CVT 0204, CVT 303009, CVT- QTC final) (all previously submitted)
- 17 Periodic Safety Update Reports and 2 Bridging Reports (all new)
- 4 other clinical studies in different indications (2 in intermittent claudication; RAN2302, RAN2320 previously submitted; and 2 new; CVT 3113, GS-US-259-0107)
- literature references

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical development of ranolazine occurred over an extended period with dose ranging studies commencing in the late 1980s and the Phase III Study CVT 3036 being completed in 2007. Early studies predated the introduction of ICH GCP guidelines. Latter studies were stated to be undertaken in accordance with ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the PK studies were provided. Table 8 shows the newly submitted studies relating to each PK topic. The previous submission contained: 13 bioavailability studies; 1 in vitro/in vivo correlation; 17 bioanalytical reports, 39 PK studies and 14 PD or PK/PD studies.

Table 8: Newly submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim of the study
PKs in healthy adults	Single dose PKs	CVT-301-22	BE of 500 mg PR tablets manufactured by Patheon compared with 500 mg PR tablets by DSM
		CVT-301-23	PK characteristics of four prototype formulations of ranolazine PR 1,000 mg QD tablets compared to 1,000 mg PR BD formulation
PK interactions	Metoprolol	CVT-301-24	Effect of ranolazine ER 750 mg BD at steady-state on the PK parameters of metoprolol
	Dronedarone	GS-US-291-0101	Interaction b/w ranolazine (375 or 500 mg BD) co-administered with dronedarone (400 mg BD) in subjects with atrial fibrillation (AF)
		GS-US-291-0112	Effect of steady-state dronedarone on the steady-state PK of ranolazine in healthy adult male subjects.
	Metformin	GS-US-259-0113	Effect of steady-state ranolazine 1,000 mg BD on the steady-state PK of metformin in subjects with type 2 diabetes mellitus (T2DM)
		GS-US-259-0143	Effect of steady-state ranolazine 500 mg BD on the steady-state PK of metformin in subjects with T2DM

PK topic	Subtopic	Study ID	Primary aim of the study
	Atorvastatin	GS-US-259-0115	Effect of steady-state ranolazine on the steady-state PKs of atorvastatin in healthy adult subjects
PK in special populations	Heart failure	GS-US-270-0101	Effect of ranolazine, compared to placebo, on diastolic function in patients with Heart failure with preserved ejection fraction (HFpEF).

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion (ADME)

- Following a single 500 mg oral dose of the formulation proposed for marketing under fasting conditions the T_{max} occurred at 4.8 hours following dosing.
- The 500 mg tablet formulations of ranolazine PR manufactured at Patheon and DSM were bioequivalent.
- The sponsor has applied for a waiver of bioequivalence studies for the 375 mg and 750 mg tablet formulations proposed for marketing. This biowaiver is in part based upon the 1,000 mg dose strength, which is used to justify the absence of BE data regarding the 750 mg dose. As the 1,000 mg dose is not part of the current application the biowaiver regarding the 750 mg dose strength is therefore not valid.
- None of the four prototype 1,000 mg once daily (QD) tablets tested had PK characteristics that were deemed suitable for once daily dosing.
- Three ranolazine metabolites (GS-448200, GS-448119 and GS-342105) were identified in healthy human plasma following 5 days dosing with 750 mg ranolazine every 12 hours.
- The activity of the various metabolites of ranolazine remains to be elucidated.
- Following 5 days of dosing with 750 mg ranolazine every 12 hours the metabolite ratios for GS-448200, GS-448119 and GS-342105 were 0.48, 0.12 and 0.31, respectively

Special populations

In patients with HF, ranolazine minimum plasma concentration (C_{min}), C_{max}, and T_{max} were 1,610 ng/mL, 5,595 ng/mL, and 22 hours, respectively.

Drug-drug interactions

Drug-drug interactions; metoprolol

Co-administration of a single dose of the CYP2D6 substrate metoprolol with ranolazine at steady state resulted in a 1.82 fold and 1.48 fold increase in metoprolol $AUC_{0\text{-}inf}$ [22]and C_{max}, respectively, compared to metoprolol monotherapy.

[22] $AUC_{0\text{-}inf}$ = Area under the plasma concentration-time curve from time 0 to infinity

Drug-drug interactions; dronedarone

Healthy subjects

Following co-administration of ranolazine (750 mg BD) with dronedarone (225 mg BD) in healthy subjects, the C_{max} and AUC_{τ} values for ranolazine were 1.2 fold higher than values obtained following administration of ranolazine alone. Similarly, the dronedarone C_{max} and AUC values increased 1.3 fold when dronedarone was co-administered with ranolazine compared to when it was administered alone.

Subjects with atrial fibrillation (AF)

The steady-state dronedarone C_{max} values were similar following both co-administration with ranolazine (375 mg and 500 mg BD) and when dronedarone (400 mg BD) was administered alone, whereas, the AUC_{0-12} was approximately 1.09 fold higher following co-administration.

Drug-drug interactions; Metformin

- In subjects with Type 2 diabetes mellitus, the mean metformin steady-state C_{max} ($C_{max,ss}$) (90% confidence interval (CI)) and AUC_{τ} values were 1.53 fold (1.41, 1.66) and 1.79 fold (1.65, 1.95) higher, respectively, when metformin (850 to 1,000 mg BD) was administered in combination with ranolazine (1,000 mg BD), compared to when metformin was administered alone.
- In subjects with Type 2 diabetes mellitus, the AUC_{τ} and C_{max} for metformin were 1.37 fold (90% CI: 1.26, 1.49) and 1.22 fold (90% CI: 1.13, 1.32) higher, respectively, when metformin (1,000 mg BD) was co-administered with ranolazine (500 mg BD) compared with metformin alone.

Drug-drug interactions; Atorvastatin

The C_{max} and AUC_{τ} values for atorvastatin (80 mg OD) when administered with ranolazine (1,000 mg BD) were 1.4 fold (90% CI: 1.23, 1.62) and 1.3 fold higher (1.17, 1.46), respectively, than when atorvastatin was administered alone.

Limitations of the PK studies

The activity of the various metabolites of ranolazine remains to be elucidated.

Summary of previously submitted PK data

Metabolic studies

- Results indicate that ranolazine is rapidly and extensively metabolised and that the major route of elimination is via metabolism followed by urinary excretion.
- The formation of CVT-2512 is dependent on both CYP2D6 and CYP3A4, whereas CVT-2514 is primarily dependent on CYP2D6.

Special populations

- Renal impairment is associated with decreased ranolazine total clearance, which is correlated with the degree of renal impairment (CVT 3016). For a decrease in creatinine clearance from 100 to 30 mL/min, the increase in ranolazine exposure is 1.84 fold, on average. Only 5 to 10% of the administered dose was excreted unchanged in urine across all degrees of renal function.
- When compared to matched healthy controls, mild hepatic impairment has no effect on ranolazine pharmacokinetics, whereas moderate impairment was associated with an increase in ranolazine exposure 1.76 fold, on average (CVT 3018).
- In population PK Study CVT 301.019-C, only four of the covariate factors examined (age, height, weight, sex, race, calculated creatinine clearance, disease stage and

administration of concomitant medications) were identified that increased ranolazine exposure. These were low body weight, renal impairment, New York Heart Association (NYHA) Class III or IV, and concomitantly administered diltiazem or a similar CYP3A4 inhibitor.

1. Exposure for a 40 kg or a 120 kg patient was, respectively 41% higher or 27% lower than for a typical subject.
2. NYHA Class III or IV increased exposure by 34%.
3. Concomitant administration of diltiazem increased exposure by 38%.
4. Exposure for subjects with calculated normalised creatinine clearance at points representing the various renal impairment categories (65, 40, 20, and 10 mL/min/1.73m^2) was, respectively, 2% (mild), 19% (moderate), 48% (severe), and 84% (very severe) higher than for subjects with normal creatinine clearance.

Drug-drug interactions

- Ranolazine metabolism is increased by the potent CYP3A inducer, rifampicin (600 mg once daily) with a more than 20 fold increase in oral clearance (CVT 301-20).
- Ranolazine administration has only minor effects on the pharmacokinetics of simvastatin and its metabolites, and on the (R) and (S) enantiomers of warfarin, indicating lack of major inhibition of CYP2C9, CYP1A2, and CYP3A4.
- Metabolite exposures relative to ranolazine are decreased by inhibitors of CYP3A4 and CYP2D6.
- Verapamil increases ranolazine concentrations approximately 2 fold and ranolazine increases digoxin concentrations 1.4 to 1.6 fold during steady state conditions. The common mechanism is P-gp, as ranolazine is a substrate for p-glycoprotein.
- Ranolazine does not modify the effect of warfarin on indices of prothrombin time to a clinically meaningful extent.

Pharmacodynamics

Studies providing pharmacodynamic data

Both of the previously unevaluated studies that contain PD results, GS-US-270-0101 and GS-US-291-0101, also contain PK data; therefore, in an effort to reduce repetition they have been summarised and included in Table 8.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

- Ranolazine is a novel anti-ischaemic drug for the treatment of angina.
- The mechanism via which ranolazine mediates its anti-anginal effects has not been fully elucidated; however, it is thought to act by inhibiting late sodium current in cardiac cells.

Summary of newly submitted PD data

- In patients with heart failure who received two bolus doses + a 30 min infusion of ranolazine, there were statistically significant decreases in resting LV end-diastolic pressure (LVEDP) (−2.13 ± 3.961 millimetres of mercury (mm Hg); p = 0.042), resting pulmonary capillary wedge pressure (PCWP) (−2.08 ± 3.166 mm Hg; p = 0.044), and

mean pulmonary artery pressure (PAP) under paced conditions (−1.76 ± 2.381 mm Hg; p = 0.016), which were not observed in placebo treated patients.

- Following 14 days treatment with oral ranolazine (1,000 mg BD), RER[23] was significantly increased (0.09 ± 0.119; p = 0.025), and VE/VCO_2[24] (−2 ± 7.2) was a significantly decreased (p = 0.034) compared to placebo. By contrast, there were no significant effects on ECG parameters or NT-proBNP.[25]
- There was a rapid onset of ranolazine effects following bolus + IV dosing in patients with atrial fibrillation (AF).

Summary of previously submitted PD data

- In patients with chronic angina, ranolazine IR significantly increased three key exercise parameters versus placebo to an equal or greater extent than atenolol: time to onset of angina, time to 1 mm ST segment depression and exercise duration without any significant effects on the rate pressure product (RPP).
- Doses of 500 mg and 1,000 mg ranolazine BD also significantly increased these three exercise parameters compared to placebo in patients with chronic angina.
- In general, doses greater than 500 mg BD ranolazine were associated with small but statistically significant decreases in End-Exercise RPP versus placebo.
- The effects of ranolazine on cardiac ventricular repolarisation characterised by increased T wave amplitude and prolongation of the QTc interval are dose- and plasma-concentration dependent.
- Clinical data in five patients with long QT syndrome (LQT) syndrome provides evidence that ranolazine may act as an inhibitor of the late sodium current (INa).
- There is no evidence that ranolazine produces a clinically significant negative inotropic effect.
- There was no clinically meaningful effect on ejection fraction in Study CVT 3021, in which ranolazine plasma concentrations were 4 to 5 times higher than in Study RAN075.
- Four out of 50 subjects co-administered 1,000 mg ranolazine BD and ketoconazole experienced QTc prolongations of greater than the 30 msec threshold, therefore the co-administration of these drugs should be carefully monitored.
- There is evidence that suggests that the maximum prothrombin time (PT_{max}) and $AUC_{0\text{-}144PT}$ are significantly increased following the co-administration of warfarin and ranolazine. Therefore, patients who are co-administered these drugs must have their prothrombin times closely monitored.

Limitations of the new PD studies

Little information is provided regarding the activity of the metabolites of ranolazine.

Comment: This was also an issue in the earlier submission (see below) and question regarding the functional activity of the metabolites was raised by the (current) clinical evaluator.

[23] RER = Respiratory exchange ratio - the difference between resting and exercise RER from baseline to Day 14
[24] VE/VCO_2 = Ventilation/carbon dioxide production ratio - the change from baseline in the difference between resting and exercise values for VE/VCO_2 at Day 14
[25] A test for B-type natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) is primarily used to help detect, diagnose, and evaluate the severity of heart failure.

Limitations of previously submitted PD studies

- No studies were conducted to examine the PD effects of ranolazine in the following groups: children below the age of 18 years, pregnant or breast feeding mothers, the ability to drive or operate machinery and different genders and racial groups.
- In addition, the PD effects of the major ranolazine metabolites are unknown and these warrant further investigation to determine whether they are pharmacologically active.
- No studies examined the effect of ranolazine on drugs that target alpha and beta adrenergic receptors, 5HT and opiate receptors.

Dosage selection for the pivotal studies

The sponsor stated that data from the ranolazine IR studies demonstrated a mean trough ranolazine plasma concentration of at least 800 ng/mL was required for efficacy and that a dose of 750 mg BD of the ranolazine PR tablet achieved this at peak and trough while 500 mg BD only achieved this at peak (data from PK Study RAN0114). Data from RAN1514 found that threshold for activity appeared to be between 602 and 1,576 ng/mL. Based on data from CVT 3031, the sponsor expected 500 mg BD to be the minimum effective dose. The Phase III program also planned to assess 1,500 mg BD to cover a threefold increase in dose, however, due to the increase in adverse events (AEs) at 1,500 mg BD, this dose was not pursued.

In the Phase III program, Study CVT 3033 assessed 750 mg BD and 1,000 mg BD while Study CVT 3037 further assessed the 1,000 mg BD dose on top of amlodipine. In Study CVT 3036, dosage was initiated with an IV infusion and followed by oral ranolazine PR dosages of 375, 500, 750 and 1,000 mg BD.

For the full evaluation of the dosage selection studies please see Attachment 2.

Efficacy

Studies providing efficacy data

There were 4 main Phase III studies of ranolazine PR in patients with chronic angina: CVT 3031, CVT 3033, CVT 3036 and CVT 3037 (Table 9). Study CVT 3031 was a dose ranging crossover study assessing the PR formulation and is discussed with the other studies providing data on dose and dose regimen (RAN072, RAN080 and RAN1514) although these latter 3 trials assessed the IR formulation (Table 10).

Table 9: Description of ranolazine clinical studies providing key efficacy data

Protocol No. Study Status	No. of Centers and Location	Study Design and Objective	No. of Patients/ Subjects	Treatment/Dosage Form/ Duration of Treatment/ Dose Regimen (n), Route	Demographics
CVT 3031 Status: Completed Study Dates: Dec 1997 to May 1999	52 sites: US, Canada, Eastern (E.) Europe	Phase 3 double-blind, randomized, placebo-controlled, 4-period, crossover study to determine the effect of ranolazine PR monotherapy to placebo on treadmill exercise duration at the time of trough ranolazine plasma concentrations (12 h postdose) when administered at 500, 1000, and 1500 mg twice a day (BID) to patients with chronic stable angina.	Planned: 203 Enrolled: 191 Completed: 168	Ranolazine PR 500 mg oral tablets; 1 week/treatment period; ranolazine 500 mg BID (n=181), 1000 mg BID (n=180), 1500 mg BID (n=187), and placebo BID (n=179).	Age: 39–85 years (y) (mean 64.3 y) Male: 140 Female: 51 Caucasian: 174 Other: 17
CVT 3033 Status: Completed Study Dates: Jul 1999 to Aug 2001	118 sites: US, Canada, E. Europe, W. Europe, Israel, Australia, New Zealand	Phase 3 double-blind, randomized, parallel-group, placebo-controlled study to determine the effect of ranolazine PR (750 or 1000 mg BID) compared to placebo on symptom-limited treadmill exercise duration at the time of trough ranolazine plasma concentrations (12 h postdose) after 12 weeks of dosing in patients with chronic angina receiving a stable dose of a single concomitant antianginal medication (diltiazem, atenolol, or amlodipine).	Planned: 810 Enrolled: 823 Completed: 731	Ranolazine PR 375 mg or 500 mg oral tablets; 12 week treatment phase followed by 2 day rebound assessment phase; ranolazine 750 mg BID (n=279), 1000 mg BID (n=275), or placebo BID (n=269).	Age: 36–92 y (mean 64.0 y) Male: 638 Female: 185 Caucasian: 803 Other: 20
CVT 3037 Status: Completed Study Dates: Jul 2004 to Feb 2005	48 sites: US, Canada, E. Europe	Phase 3 double-blind, randomized, parallel-group, placebo-controlled study to determine the effect of ranolazine PR (1000 mg BID) compared to placebo on angina frequency during 6 weeks of double-blind dosing in patients with chronic angina who remained symptomatic despite treatment with amlodipine at a dose of 10 mg daily.	Planned: 500 Enrolled: 565 Completed: 552	Ranolazine PR 500 mg oral tablets; 1 week at 500 mg BID (n=281) or placebo BID (n=283) followed by 6 weeks at 1000 mg BID (n=280) or placebo BID (n=281).	Age: 39–84 y (mean 61.7 y) Male: 407 Female: 158 Caucasian: 558 Other: 7
CVT 3036 Status: Completed Study Dates: Oct 2004 to Feb 2007	442 sites: US, Canada, E. Europe, W. Europe, Israel, So. Africa	Phase 3 double-blind, randomized, parallel-group, placebo-controlled, study to determine whether ranolazine was superior to placebo for reducing the rate of CV death, MI, or recurrent ischemia during long-term treatment of patients with non-ST elevation ACS receiving standard therapy.	Planned: 6500 Enrolled: 6560 Completed: 6216	Ranolazine IV infusion for up to 96 h followed by 375 mg or 500 mg PR oral tablets at doses of 375, 500, 750, or 1000 mg BID through the end of the study.	Age: 24–99 y (mean 63.5 y) Male: 4269 Female: 2291 Caucasian: 6241 Other: 319

Table 10: Description of ranolazine clinical studies providing supportive efficacy data

Protocol No. Study Status	Location of Centers (n)	Study Design and Objective	No. of Patients/ Subjects	Treatment/Dosage Form/ Duration of Treatment/ Dose Regimen (n), Route	Demographics
RAN080 Status: Completed Study Dates: Jan 1992 to May 1993	International (9)	Phase 2 double-blind, double-dummy, randomized, placebo-controlled, 3-way, crossover with preceding single-blind placebo washout period: antianginal efficacy and safety of ranolazine IR 400 mg tid versus (vs) atenolol 100 mg once daily or placebo.	Planned: 108 Enrolled: 158	Ranolazine IR 400 mg capsules; 1 week per treatment period; ranolazine 400 mg tid (n=155), atenolol 100 mg once daily (n=154), and placebo tid, po (n=154).	Age: 41–77 (mean 59.3 y) Males: 140 Females: 18 Caucasian: 156 Other: 2
RAN072 Status: Completed Study Dates: Dec 1989 to Apr 1991	International (4)	Phase 2 double-blind, randomized, placebo-controlled, single-dose, crossover study in patients with severe CAD remaining symptomatic on approved doses of diltiazem or beta blocker (metoprolol, atenolol or propanolol): safety, efficacy, tolerability of 4 different doses of ranolazine and relation between dose and plasma level.	Planned: 106 Enrolled: 106	Ranolazine IR 10 mg, 60 mg, 120 mg, or 240 mg capsules; single-dose treatment periods with 2–7 day washout between periods; ranolazine 10 mg (n=24), 60 mg (n=26), 120 mg (n=29), or 240 mg (n=27), po; or placebo (n=106), po.	Age: 28–73 y (mean 58.2 y) Male: 81 Female: 25 Caucasian: 106 Other: 0
RAN1514 Status: Completed Study Dates: Jun 1992 May 1993	US (42) International (7)	Phase 2 randomized, extended-period, Latin square design in patients with chronic angina pectoris in 2 phases: (1) single-blind, placebo, qualifying phase; (2) placebo-controlled, double-blind, treatment phase with 4 treatment sequences, 4 treatments, and 5 double-blind periods: 3 dosing regimens of IR ranolazine vs placebo with respect to, at trough and peak, ETT time to onset of angina, duration of exercise, and time to 1 mm ST-segment depression.	Planned: 240 Enrolled: 318	Ranolazine IR 267 mg or 400 mg capsules; 1 week per treatment period/267 mg tid, po (n=305), 400 mg tid, po (n=309), 400 mg BID, po (n=306); and placebo tid, po (n=310).	Age: 33–85 y (mean 64.2 y) Male: 230 Female: 88 Caucasian: 273 Other: 45

For the full clinical evaluation of efficacy please see Attachment 2.

Evaluator's conclusions on efficacy

Overall, 8,653 subjects from the 7 main controlled studies of ranolazine were included in the primary efficacy analyses (4,881 with ranolazine and 4,582 with placebo). The number of patients who received the varying doses of ranolazine PR in the four studies (CVT 3031, CVT 3033, CVT 3036 and CVT 3037) is shown in Table 11. All studies allowed concomitant anti-anginal medications except for CVT 3031 which was the only study of ranolazine as monotherapy.

Table 11: Dosing information for studies CVT 3031, CVT 3033, CVT 3037 and CVT 3036

Study	Placebo	No. of Patients by Ranolazine PR Dose			
		500 mg BID	750 mg BID	1000 mg BID	1500 mg BID
CVT 3031[a]	179	181	--	180	187
CVT 3033	269	--	279	275	--
CVT 3037	283	--	--	281	--
CVT 3036[b]	3273	--	--	3268	--
Total	**4004**	**181**	**279**	**4004**	**187**

a CVT 3031 was a crossover study in which patients received more than 1 treatment

b Oral dosing in CVT 3036 was preceded by up to 96 hours of IV ranolazine

Source: CSRs for CVT 3031, CVT 3033, CVT 3037, and CVT 3036

Early development work was with the IR formulation of ranolazine and noted anti-anginal and anti-ischaemic effects with 240 mg at peak (RAN072) and similar effects to atenolol 100 mg once daily with ranolazine IR 400 mg TDS at peak levels (RAN080). Study RAN1514 showed that ranolazine IR 800 mg (267 mg TDS or 400 mg BD) or 1,200 mg per day had positive effects at peak but not at trough. These results led to the development of the ER formulation. Other early studies in the dossier did not provide useful information on dose response or efficacy: RAN1515, RAN020 and RAN1513 had doses lower than 800 mg per day which were not effective; RAN054 and RAN012 did not provide data of sufficient robustness for interpretation; and RAN1490 was prematurely discontinued with no data included.

Study CVT 3031 provided the main data on dose response with the proposed extended release formulation. This placebo controlled, crossover study found that 1 week of monotherapy with ranolazine SR, at doses of 500 mg BD, 1,000 mg BD and 1,500 mg BD, significantly improved exercise duration at trough and at peak levels in subjects (175 evaluable) with chronic stable angina. There was a dose response with more improvement in exercise duration at higher doses and at peak compared to trough levels. Results were supported by an improvement in time to angina onset and time to 1 mm ST segment depression at trough and peak. There was only a small increase in the difference in mean exercise duration compared to placebo for the 1,500 mg BD dose (55.5 sec) compared to the 1,000 mg BD dose (50.1 sec). In addition, the 1,500 mg dose had a disproportionate increase in AEs. Consequently, 1,000 mg BD was chosen as the maximal dose for further studies.

There were significant limitations with Study CVT 3031: the design was crossover instead of parallel group, the treatment duration was 1 week rather than 6 weeks, the run-in period was shorter than recommended, and subjects could have been included too soon after revascularisation (only 2 months instead of the recommended 6 months). In addition, there were no washouts between periods and, whilst there was no statistically significant interaction on assessment of carryover, the data from the first period found no improvement in exercise duration at trough. The sponsor claims this was a chance finding. Whilst it is possible there is no true effect at trough, given positive data in CVT 3033 discussed below, the evaluator agrees that the lack of a significant finding at trough in the first period could be a chance finding. The evaluator believes that given these findings, the crossover design, and the short treatment duration, Study CVT 3031 can only be classed as in initial therapeutic study and not pivotal (as claimed by the sponsor). Furthermore, as CVT 3031 was the only study of ranolazine monotherapy, the evidence provided is not adequate to support an indication for ranolazine as monotherapy treatment in chronic angina.

Study CVT 3031 established ranolazine PR 1,000 mg BD as the maximum effective dose. The minimum effective dose was not clearly delineated in this study as 500 mg BD was effective although it did only increase exercise duration by 23.8 sec. Plasma ranolazine levels of 848 ng/mL resulted in a significant effect on exercise duration (Study CVT 3031, 500 mg PR) while a level of 503 ng/mL (Study RAN072, 120 mg IR) did not (Table 12). This association between ranolazine dose, peak and trough plasma levels and exercise duration was used by the sponsor to establish the minimum effective dose. It is unclear, however, whether a dose lower than 500 mg BD of the PR formulation would have given plasma levels sufficient for efficacy and such a dose was not assessed in the dose ranging studies.

Table 12: Association between ranolazine dose, trough, peak plasma levels, exercise duration in the ranolazine IR and PR studies demonstrating efficacy

Study No. (formulation)	RAN072 (IR)				RAN1514 (IR)			RAN080 (IR)	CVT 3031 (PR)	CVT 3033 (PR)		CVT 3031 (PR)	
Dose, mg:	10 sd	60 sd	120 sd	240 sd	267 tid	400 BID	400 tid	400 tid	500 BID	750 BID	1000 BID	1000 BID	1500 BID
Trough													
ETT duration, sec difference from placebo[a,b]	NA	NA	NA	NA	11.4	10.8	4.2	NA	23.8	23.7	24.0	33.7	45.9
p-value	—	—	—	—	NS	NS	NS	—	0.003	0.030	0.029	< 0.001	< 0.001
Mean plasma concentration,[c] ng/mL	NA	NA	NA	NA	317	235	514	NA	848.9	1577.6	2164.7	1959.2	3241.0
Peak													
ETT duration, sec Difference from placebo[a,b]	9.6	13.7	−1.9	36.6	23.4	19.2	19.2	51.0	29.3	34.0	26.1	50.1	55.5
p-value	NS	NS	NS	0.004	< 0.01	0.013	0.012	< 0.001	< 0.001	0.001	0.016	< 0.001	< 0.001
Mean plasma concentration,[c] ng/mL	39	213	503	880	1346	1882	2128	1741	1122.6	2031.1	2607.1	2476.0	3930.5

a Least squares mean difference from ANOVA models.
b For Studies RAN080 and RAN1514, time to onset of angina (the primary efficacy endpoint in those studies) is substituted for ETT duration.
c Plasma concentrations are given as ranolazine free base.
sd = single-dose; NA = not available; NS = not statistically significant

Study CVT 3033 was the pivotal Phase III efficacy study in the dossier. It was a 12 week, placebo controlled, parallel group, add-on study of ranolazine PR (750 mg BD and 1,000 mg BD) in 791 subjects with chronic stable angina pectoris treated with a single anti-anginal agent (diltiazem 180 mg once daily, atenolol 50 mg once daily or amlodipine 5 mg once daily). The study design met EMA requirements for investigation of anti-anginal medicinal products in stable angina.[26]

The anti-anginal effect of ranolazine was found for both doses with a statistically significant increase in exercise treadmill (tolerance) testing (ETT) duration at trough levels with an improvement of about 24 seconds for both doses. The results were supported by statistically significant improvements in secondary endpoints of ETT duration at peak, time to angina onset at peak and trough, angina episodes and nitroglycerin use. Overall, treatment effects were greater at peak compared to trough and the anti-ischaemic effect, as measured by time to 1 mm ST segment depression, was only significantly different to placebo at peak. A response to ranolazine was evident after 2 weeks of treatment, there was no evidence of rebound and treatment effect had been lost two days after ceasing treatment.

While Study CVT 3033 was positive, there was only a small improvement in exercise duration of 24 seconds. In addition, the doses of 750 mg BD and 1,000 mg BD had similar efficacy (exercise duration: 23.7 versus 24.0 sec; time to onset of angina: 143.5 versus 139.7 sec; and time to 1 mm ST segment depression 143.3 and 144.2 sec for 750 and

[26] CPMP/EWP/234/95/rev. 1 (1 June 2006); Guideline on the clinical investigation of anti-anginal medicinal products in stable angina pectoris.

1,000 mg, respectively) and dose response was not evident. It was only on the secondary endpoints of angina episodes per week (750 mg 2.47 versus 1,000 mg: 2.13) and nitroglycerin use (2.11 versus 1.76) that some modest benefit of the higher dose was seen. Background therapies appeared to influence exercise duration with only a very small improvement in ETT duration at trough for those on atenolol (7.5 sec). While the efficacy of ranolazine was demonstrated in this add-on study, the background anti-anginal therapy had not been optimised prior to enrolment (doses given were: atenolol 50 mg once daily, amlodipine 5 mg once daily and diltiazem 180 mg once daily) so the add on effect of ranolazine on treatment with higher doses of these medications is unknown.

Study CVT 3037 was a placebo controlled, parallel group study of ranolazine SR 1,000 mg BD in 565 patients with chronic angina who were symptomatic despite maximal dose of amlodipine (10 mg once daily) (and long acting nitrate (LAN) in 45%). After 6 weeks of treatment, ranolazine 1,000 mg BD resulted in a statistically significant reduction in angina attacks per week compared to placebo (trimmed mean 2.82 versus 3.24) and less nitroglycerin use (1.99 versus 2.62). This benefit was modest with less than one angina attack per week reduction. There was no significant difference on 4 of 5 items on the Seattle Angina Questionnaire (SAQ) as only angina frequency was reduced significantly. It is noted that the SAQ had not been validated for use in Eastern European countries (97% of study subjects) and the main outcomes were based on patient reports (diaries) which may be subject to patient perception, however, the study was blinded and placebo controlled which would control for this potential bias. The study duration was short (6 weeks), the primary efficacy endpoint was not an exercise based variable as recommended in the guideline,[26] and concomitant anti-anginal treatment had not been optimised so the patient population does not match the proposed target population. Therefore the evidence from this study is only considered supportive.

Study CVT 3036 was a large cardiovascular outcome study which enrolled 6,560 subjects with a moderate to high risk of cardiovascular events and non-ST elevation acute coronary syndrome (ACS). Ranolazine or placebo treatment was given as add-on to standard therapy and after an initial IV ranolazine infusion for up to 96 hours, oral ranolazine SR was continued at a dose of 1,000 mg BD (or 750 mg, 500 mg or 375 mg BD if adverse events or renal insufficiency). At the end of the study, 83% of ranolazine subjects remained on the 1,000 mg dose. The study did not meet its primary endpoint. Ranolazine treatment did not reduce the risk of the composite primary endpoint of cardiovascular death, myocardial infarction (MI) or recurrent ischaemia compared to placebo over the entire study duration (RR = 0.92, 95% CI: 0.83, 1.02 p = 0.11) nor was there a significant effect in the early (30 days post randomisation) or later period.

While there was no effect on cardiovascular death or MI individually, there was some evidence for reduction in recurrent ischaemia (defined as worsening angina or ischemia requiring additional therapy and severe recurrent ischemia showing ECG changes, leading to hospitalisation, or prompting revascularisation) with a RR of 0.86 (95% CI: 0.76,0.98 p = 0.03). At Month 4, there was a small reduction in the mean number of concomitant anti-anginal medication used (1.7 placebo versus 1.6 ranolazine) and a small (though statistically significant) improvement in the angina frequency score on the SAQ. The clinical relevance of these small changes would be modest at best and there was no improvement on the physical limitation scale of the SAQ.

Subgroup analysis found subjects with a prior history of chronic angina (54%) had a better response to ranolazine treatment with a small improvement on the SAQ and in exercise duration on ETT (32 sec.). It was noted, however, that these analyses were post-hoc and the ETTs were not standardised with variable results noted on the tests used. The evaluator concludes that Study CVT 3036 did not support the use of ranolazine in the treatment of ACS though it did provide modest supportive anti-anginal efficacy data in chronic angina patients.

Overall, subgroup analysis for subjects with obstructive lung disease, congestive heart failure (CHF) (NYHA class I and II) and diabetes found no significant differences compared to those without the disease. The effect in those aged 65 years or more was also not notably different to the younger age group. The efficacy of ranolazine in women was consistently less than in men however some efficacy was demonstrated in post-hoc subgroup analysis of ischaemia based endpoint in Study CVT 3036. None of the studies provided sufficient data for analysis in non-Caucasian populations so no conclusions can be made about other racial groups.

None of the clinical trials with exercise based endpoints reported improvement in exercise capacity in terms of metabolic equivalent of the task (METs) which is the recommendation of the guideline.[26] The use of METs would have assisted in providing a standard measure regardless of the protocol or test used and would have assisted in Study CVT 3036 where there was variability in ETTs performed.

There was no new efficacy data submitted to support the proposed indication.

In the newly submitted studies, GS-US-259-0107 demonstrated an effect of ranolazine ER 500 mg BD on haemoglobin A1c (HbA1c) after 12 weeks of treatment (0.53% reduction over placebo) in subjects with type 2 diabetes mellitus. There was however no significant effect on serum glucose (fasting or 2 hour postprandial). The sponsor has not made specific claims in the PI with respect to this study. The proposed wording in the PI, which the evaluator believes is satisfactory, is:

Ranexa produces small reductions in HbA1c in patients with diabetes, the clinical significance of which is unknown. Ranexa should not be considered a treatment for diabetes.

Study CVT 3041 failed to find validity for the WISQ in women with chronic angina and Study CVT 3113 found that in these subjects who had undergone cardiac catheterisation for an invasive EP procedure, ranolazine IV had no effect on the EP parameters and in particular no effect on atrial refractoriness.

The efficacy data in the dossier support treatment with concomitant anti-anginals although this had not always been optimised prior to randomisation. There are insufficient data on the use of ranolazine as monotherapy. Data indicate that the 750 mg BD dose is likely to be as efficacious as the 1,000 mg BD dose.

Efficacy was consistent across age subgroups. There were gender differences in ETT parameters with a notably lower effect in females. While there was a reduction with ranolazine in average weekly angina attacks and nitroglycerin consumption compared to placebo in females the sponsor has been requested to provide more information and include a comment in the PI relating to efficacy in females.

Safety

Studies providing safety data

As of July 2012, the ranolazine clinical program has included 11,210 subjects (healthy, chronic angina, non-ST elevation ACS or type 2 diabetes mellitus) with 7,451 who have received ranolazine IV, IR or PR formulations. Safety data was presented from an integrated safety database (ISD) consisting of 71 trials completed by August 2006 (14 Phase II/III studies with IR or PR ranolazine, 5 uncontrolled open label studies, 49 Phase I and clinical pharmacology studies, plus studies CVT 3024, CV 301-18 and CVT 301-20). Sixteen early pharmacology studies were not included due to limited exposure information. A further 14 studies were not integrated into the ISD (Table 13).

Table 13: Summary of clinical trials by ranolazine formulation

	Number of Subjects/Patients[a]					
	Ranolazine Formulation			Total Number Exposed		
Completed Trials	IR	PR	IV	Ranolazine	Placebo	All[b]
Integrated Safety Database (ISD)[c]	1299	2116	101	3463	1829	3723
16 Early Studies[d]	86	0	151	237	159	304
Study CVT 3036[e]	0	3194	3266	3268	3273	6541
14 Additional Studies[f]	0	449	50	488	92	552
Total of All Study Drug-treated Subjects/Patients	1385	5759	3568	7456	5353	11120

a Number of subjects/patients reflects number of subjects/patients who received at least 1 dose of study drug.

b For studies with a crossover design, subjects/patients were only counted once in the overall total number of subjects/patients columns.

c 71 integrated studies.

d The following early studies were not integrated into the ISD: RAN001, RAN002, RAN003, RAN003B, RAN004, RAN005, RAN006A, RAN007, RAN008, RAN010, RAN011, RAN012, RAN014, RAN055, RAN070, and RAN1789.

e Patients were initially treated with IV ranolazine and then switched to oral ranolazine.

f The following studies have not been integrated into the ISD: CVT 3113, CVT 3114, CVT 301-19, CVT 301-22, CVT 301-23, CVT 301-24, CVT 3041, GS-US-259-0107, GS-US-259-0113, GS-US-259-0115, GS-US-259-0143, GS-US-270-0101, GS-US-291-0101, and GS-US-291-0112.

A subset of the ISD was the Phase II and III controlled angina studies trials with the PR formulation (Studies CVT 3033, CVT 3037, CVT 3031 and RAN2240). This included 1,030 patients treated with ranolazine PR and 738 with placebo. The Phase III Study CVT 3036 in ACS, of whom 54% had a history of angina, included 3,268 ranolazine and 3,273 placebo treated subjects. These two populations provided the most relevant safety information. Long term safety data comes from three open label safety extension studies (CVT 3024, CVT 3032 and CVT 3034).

Patient exposure

The mean duration of exposure to ranolazine PR was 559 days with a total exposure was 3,240 subject-years. In the controlled Phase II/III ranolazine PR subset of 1,030 patients, the mean exposure duration was 61 days for ranolazine and 52 days for placebo. In Study CVT 3036, the mean exposure (IV and oral dosing) was 279 and 297 days in the ranolazine and placebo groups, respectively (Table 14). In this study, the majority of patients (83% versus 89%) commenced on the 1,000 mg BD oral dose and this was the final dose in 83% and 89% of the ranolazine and placebo groups, respectively.

Of note, in the ISD, the mean exposure duration to ranolazine was 387 days while to placebo was 28 days.

Comment: Due to the differing exposure duration, comparison of AE rates between ranolazine and placebo in the ISD will be biased.

Table 14: Mean exposure in the Phase II/III PR controlled angina studies, their open label long term follow up studies ISD and Study CVT 3036

Phase 2/3 PR Controlled Angina Studies		Open-Label Long-Term Follow-up			ISD Database (IR, PR, IV)		CVT 3036 (IV + PR)	
Placebo N = 738	Ranolazine N = 1030	CVT 3024 Ranolazine N = 9	CVT 3032 Ranolazine N = 143	CVT 3034 Ranolazine N = 1108	Placebo N = 1829	Ranolazine N = 3463	Placebo N = 3273	Ranolazine N = 3268
52 days	61 days	314 days	1403 days	823 days	28 days	387 days	297 days	279 days

Demographics: In the Phase II/III controlled angina studies and CVT 3036, most subjects were male (75% and 65%, respectively), aged < 75 years (90% and 82%) and Caucasian (97% and 95%). As expected in these patient populations, comorbidity was frequent, in particular previous MI (64% and 35%), hypertension (72% and 73%), congestive heart failure (34% and 17%) and diabetes (22% and 34%)(Table 15).

Table 15: Baseline characteristics; Phase II/III PR controlled angina studies and CVT 3036*

	Number (%) of Patients					
	Phase 2/3 Controlled Angina Studies			Study CVT 3036		
	Treatment			Treatment		
Parameter	Placebo (N = 738)	Ranolazine (N = 1030)	All (N = 1768)	Placebo (N = 3273)	Ranolazine (N = 3268)	All (N = 6541)
Underlying Disease						
Previous Myocardial infarction (MI)	480 (65)	645 (63)	1125 (64)	1094 (33)	1114 (34)	2208 (34)
Hypertension	548 (74)	725 (70)	1273 (72)	2405 (73)	2384 (73)	4789 (73)
Previous Coronary artery bypass graft (CABG)	122 (17)	190 (18)	312 (18)	379 (12)	389 (12)	768 (12)
Congestive heart failure (CHF)	252 (34)	343 (33)	595 (34)	557 (17)	537 (16)	1094 (17)
Diabetes mellitus	156 (21)	231 (22)	357 (22)	1117 (34)	1098 (34)	2215 (34)
Previous ventricular arrhythmia	92 (13)	124 (12)	216 (12)	124 (4)	119 (4)	243 (4)
Unstable angina	187 (25)	260 (25)	447 (25)	1524 (47)	1535 (47)	3059 (47)

* All patients dosed.

Safety issues with the potential for major regulatory impact

Cardiovascular safety

A population PK/PD analysis (CVT 303) of 1,308 patients and healthy volunteers noted the slope of the population concentration QTc relationship to be 2.4 msec per 1,000 ng/mL plasma ranolazine concentration. This analysis found that QTc prolongation was more marked in subjects with mild and moderate hepatic impairment compared to those with angina (change from baseline of 6.62 and 7.42 msec/1,000ng/mL respectively versus. 2.4 msec/1,000ng/mL).

Comment: These risks in mild to moderate liver impairment have been reflected in the contraindications and precautions sections of the PI (moderate to severe impairment being a contraindication and mild impairment a precaution with careful dose titration).

Data from Study CVT 3036 was used to assess the relationship between QTcF[27] and mortality using Cox regression. Baseline QTc was found to be a significant predictor of mortality with a RR of 0.5% (95% CI: 0.1-0.9%, p < 0.001) per 1 msec increase in baseline QTcF in the ranolazine group and 0.7% (95% CI: 0.4-1.1%) in the placebo group. There was no significant difference between the treatment groups (p = 0.36).

Symptomatic documented arrhythmias (those that led to prolonged hospitalisation or were documented by ECG) were adjudicated by the Clinical Events Committee (CEC) in Study CVT 3036 and there was no significant difference between groups (ranolazine 3.0% versus placebo 3.1%, p = 0.84). Subjects in CVT 3036 also had 7 days of Holter monitoring from randomisation and ranolazine subjects had less clinically significant arrhythmias during this period (79.9% versus 87.4%, p < 0.001) including less ventricular tachycardia (VT) ≥ 3 beats (52.1% versus 60.6%) and SVT (44.7% versus 54.9%) (Table 16). Further evaluation after unblinding found that there were fewer episodes of ventricular tachycardia lasting ≥ 8 beats (5.2% versus 8.3%) and this risk was less in the high risk groups of Thrombolysis in Myocardial Ischemia (TIMI) risk score 5-7, LV ejection fraction ≤ 40%, QTc ≥ 450 msec and prior heart failure (Table 17).

Table 16: Incidence and frequency of clinically significant arrhythmias during the 7 day continuous ECG (Holter) monitoring (CVT 3036, all patients dosed)

	Placebo (n=3273)	Ranolazine (n=3268)	P-value
Number of Patients with Holter Data	3189	3162	
Incidence of Clinically Significant Arrhythmias	2786 (87.4%)	2525 (79.9%)	<.001 (CMH)
Incidence of Any Clinically Significant Arrhythmias			
Any VT>=100 bpm >= 3 beats	1934 (60.6%)	1646 (52.1%)	
Any SVT>=120 bpm	1752 (54.9%)	1413 (44.7%)	
New-onset Atrial fibrillation	75 (2.4%)	55 (1.7%)	
Any Bradycardic episode	1485 (46.6%)	1257 (39.8%)	

Note: P-value from CMH general association test stratifying by the intention for early invasive management. Frequencies are based on actual number of events reported for each patient. No adjustment was made for patients who wore Holter device longer or shorter than the protocol specified 7 days.

Derived from study report for CVT 3036 Addendum 2, Table 2.1

Table 17: Incidence of VT ≥ 8 beats and sudden cardiac death in selected high risk groups (CVT 3036, all patients dosed)

	VT Lasting at least 8 Beats			Sudden Cardiac Death		
	Ranolazine	Placebo		Ranolazine	Placebo	Relative Risk (ranolazine:placebo) (95% CI)
	Number of Events (%)		p-value[a]	Number of Events (Kaplan-Meier Estimate % incidence at 12 months)		p-value[b]
TIMI Risk Score						0.90 (0.51, 1.6)
5–7	29/654 (4.4)	58/653 (8.9)	0.001	22 (3.5)	25 (3.9)	p = 0.73
Prior Heart Failure						0.85 (0.49, 1.5)
Yes	28/547 (5.4)	51/522 (9.3)	0.013	23(4.1)	28 (4.3)	p = 0.57
LV Ejection Fraction						0.49 (0.22, 1.1)
≤ 40%	26/289 (8.8)	48/286 (16.6)	0.004	9 (2.7)	17 (4.9)	p = 0.08
QTc Interval at Baseline						0.69 (0.35, 1.3)
≥ 450 ms	33/600 (5.6)	63/591 (10.5)	0.002	15 (3.0)	22 (3.0)	p = 0.26

a CMH test stratifying by intention for early invasive management.
b Log-rank test stratifying by intention for early invasive management.

There were two cases of VT with appearance of TdP, one in each treatment group. As discussed, above, in post-marketing surveillance there were 10 cases of torsades de pointes or polymorphic VT to 7 July 2010 with the 5 well documented cases having

[27] QTcF = QT interval using Fridericia correction for heart rate (QT/RR⅓)

alternative explanations such as concomitant us of other QT prolonging medications. Four cases did not have ECG findings consistent with TdP and one case had insufficient details.

Comment: The QTc effects of ranolazine are dose dependent. Reassuringly, in the clinical development program has found no associated increased risk of arrhythmias or mortality. The review of post-marketing data on VT/TdP should be updated.

Post-marketing data

Ranolazine was approved in the US in January 2006 and in the EU in July 2008. To 31 January 2012 the sponsor estimated the cumulative exposure to ranolazine was 562,408 patients in the US. Based on sales figures in the EU, it was estimated the cumulative exposure in the EU was 871,178 patient-months.

The sponsor stated that there have been 15 cumulative safety reviews to assess possible safety signals. These have covered pulmonary fibrosis, myasthenic syndrome, rhabdomyolysis and myalgia, dysuria and similar conditions, feeling drunk and similar neurologic events, ranolazine-tacrolimus drug-drug interaction, medication residue, QT prolongation and torsades de pointes, psychiatric disorders, renal failure and related disorders, nervous system disorders, drug interactions, angioedema, and rash and pruritus.

Following these reviews the actions taken included:

- Inclusion in the ranolazine core company data sheet (CCDS) of: dysuria and urinary retention, coordination abnormal, gait disturbance hallucination, confusional state, headache, syncope, tremor, paraesthesia, hypoesthesia, angioedema, rash and pruritus.
- Lowering the starting and maintenance dose of simvastatin when co-administered with ranolazine. Addition of text limiting the dose of simvastatin used concomitantly with ranolazine to 20 mg once daily.
- Addition of text regarding the potential need for dose adjustment of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range when co-administered with ranolazine. Examples of relevant sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range to be included in the CCDS are simvastatin, lovastatin, cyclosporine, tacrolimus, and sirolimus.

Due to the risk of increased statin concentrations, the risk of skeletal muscle complaints was assessed. No increased risk was noted from clinical trial data. However, there were post-marketing reports of musculoskeletal AEs including rhabdomyolysis with a temporal association with ranolazine therapy. The risk was seen with simvastatin doses lower than 80 mg per day.

As of 7 July 2010 there were 10 spontaneous reports of torsades de pointes (TdP) polymorphic VT with estimated rates of 0.2 cases per 10,000 patients in the US and 0.1 per 10,000 patient months in the EU. Five of the cases were well documented cases and had alternative explanations. There was no proposed change to the CCDS proposed following this review.

Comment: As these data are 5 years old, an update on post-marketing TdP and VT reports is recommended.

The review of nervous system disorders found that dizziness, headache, syncope, tremor, paraesthesia and hypoesthesia should be included on the core data sheet, with insufficient evidence for myoclonus and involuntary muscle contractions. Based on the reviews there was no change to the CCDS for pulmonary fibrosis, myasthenic syndrome, medication residue in stool or ostomy bag. There was insufficient evidence available for the inclusion of psychiatric disorders. Ranolazine requires careful dose titration in patients with renal

impairment and a maximum dose of 500 mg BD in patients with severe renal impairment. There were no further changes recommended relating to renal failure and related disorders. There were no additional drug interactions or new safety concerns associated with known drug interactions identified.

Comment: The dossier included periodic safety update reports (PSURs) which only covered up to 26 January 2013 (PSUR-mar-3). Current post-marketing data covering the next two years should be submitted for evaluation.

Evaluator's conclusions on safety

The ranolazine clinical program was large and included 11,120 subjects with 7,456 who have received ranolazine IV, IR or PR formulations. Data were presented from the integrated safety database (ISD), which consisted of 71 trials and including 3,463 ranolazine and 1,829 placebo subjects. The most relevant data comes from a subset of the ISD, termed Phase II/III angina studies, which contained 4 controlled, chronic angina studies with the PR formulation and 1,030 ranolazine ER and 738 placebo subjects. Safety data was also presented from the cardiovascular outcome study in non-ST elevation ACS, CVT 3036, which included 3,268 ranolazine and 3,273 placebo treated subjects, of whom 54% had a history of chronic angina.

Exposure to ranolazine was from a dose of 10 mg to 2250 mg BD with a total exposure in the ISD of 3,669 patient-years and mean duration of 559 days. In the controlled Phase II/III angina dataset, the mean exposure was 61 days and in Study CVT 3036 the mean exposure was 279 days. In CVT 3036, while dose adjustment was allowed, 83% received 1,000 mg BD as their final dose. In the Phase II/III dataset ranolazine subjects were predominantly male (76%), Caucasian (96%), < 75 years old (89%), with a history of MI (63%) and hypertension (70%).

Ranolazine resulted in a higher rate of AEs than in placebo treated subjects (38.3% versus 27.6% from the Phase II/III dataset, and 76% versus 73% from CVT 3036). Constipation, dizziness, nausea, headache, asthenia, vomiting, hypotension, fatigue were the main AEs which were more frequent with ranolazine. Syncope was also more frequent (0.6% versus 0%) in the Phase II/III dataset although it occurred at the same rate (2%) in CVT 3036.

Ranolazine treated subjects had a higher rate of discontinuation due to AEs (6.3% versus 3.0% in Phase II/III dataset and 13% versus 8% in CVT 3036). The most frequent AEs leading to discontinuation were nausea, constipation, vomiting, dizziness and headache. Discontinuation due to cardiac disorders was similar between groups.

Doses of ranolazine above 1,000 mg BD were not tolerated with a disproportionate increase in AEs with doses of 1,500 mg BD. The main AEs with a dose dependent incidence were constipation, dizziness, nausea and asthenia. The dose of 1,000 mg BD resulted in a small but noticeable increase in AEs and discontinuations due to AEs compared to the 750 mg dose. Following IV administration of ranolazine, withdrawal increased at plasma levels > 5,000 ng/mL and at high levels blurred vision, diplopia, vasovagal syncope, somnolence and lethargy were observed. Doses of 1,000 mg BD resulted in plasma levels of 2,100 to 2,600 ng/mL and 750 mg BD in levels of 1,600 to 2,000 ng/mL (Study CVT 3033, Table 18). Consequently, ranolazine has a notably low safety margin.

Table 18: CVT 3033 Ranolazine plasma concentrations (ng/mL) at Week 12 at trough and peak during the double blind phase: safety population

		Ranolazine SR 750 mg	Ranolazine SR 1000 mg	Ranolazine SR 1000 mg vs Ranolazine SR 750 mg
Trough	Mean (or mean difference)	1577.6	2164.7	592.0
	SE (or SE of mean difference)	71.0	89.2	110.1
	P-value	-	-	<0.001
Peak	Mean (or mean difference)	2031.1	2607.1	567.0
	SE (or SE of mean difference)	78.8	90.0	118.0
	P-value	-	-	<0.001

Note: Data summarized above are located in Tables 3.5.0, 3.5.0.1, 3.6.0 and 3.6.0.1.

There were 3 open label safety studies which included 1,251 subjects at doses of 500 to 1,000 mg BD, for a median duration of 1.2 years for the 1,108 subjects in Study CVT 3024. AEs were consistent with the controlled study data.

Ranolazine treatment did not increase the risk of mortality (RR = 0.99 95% CI: 0.80, 1.22 p = 0.91) or of sudden cardiac death (RR = 0.87, 95% CI: 0.61, 1.24; p = 0.43) and this was consistent across subgroups. The incidence of serious adverse event (SAEs) was slightly higher in ranolazine treated subjects (5.4% versus 3.0%) in the Phase II/III dataset but similar in CVT 3036 (34% for both groups). As would be expected in this patient population, the main SAEs in CVT 3036 were cardiovascular and these occurred at a similar frequency between groups. SAEs of syncope were slightly more frequent in ranolazine subjects (0.4% versus 0% in Phase II/III angina studies, and 1.0% versus 0.7% in Study CVT 3036), however in CVT 3036 the incidence of arrhythmias was 3% in both groups.

Laboratory investigations found an increase in serum creatinine of 0.1 mg/dL in the Phase II/III studies and shift from normal to high creatinine in 16% of ranolazine subjects compared to 11% placebo in CVT 3036. Ranolazine treatment resulted in a statistically significant reduction in HbA1c in diabetic patients of 0.43% (placebo subtracted) after 4 months of treatment and 0.24% after 8 months, together with a small reduction in non-fasting glucose levels in Study CVT 3036. A reduction in HbA1c was also seen in CVT 3033 and GS-US-259-0107. In this latter study, which assessed the metabolic effects more definitively in patients with type 2 diabetes mellitus, there was no effect on glucose levels. The fact that ranolazine is not a treatment for diabetes has been included in the PI.

Ranolazine did not affect heart rate or blood pressure in doses up to 1,000 mg BD. One of the major safety issues is the dose dependent increase in QTc. In the Phase II/III studies there was a 2 to 7 msec increase in QT interval at doses of 500 to 1,000 mg BD and the population concentration-QTc relationship was found to be 2.4 msec per 1,000 ng/mL plasma ranolazine concentration. There was a more marked prolongation in subjects with hepatic impairment. Despite this prolongation, there was no increased risk of mortality in CVT 3036, no increase in symptomatic documented arrhythmias (ranolazine 3.0% versus placebo 3.1%, p = 0.84) and 7 days of Holter monitoring post-randomisation found a reduced risk of clinically significant arrhythmias (79.9% versus 87.4%, p < 0.001). This lower arrhythmia risk was maintained across high risk groups.

AE risk increased with increasing age and there was a higher discontinuation due to AEs, rising to 21%, in the elderly ≥ 75 years. Males and females had similar AE incidence apart from more nausea and vomiting in women. Subjects with a body weight under 60 kg also had an increased risk of AEs, particularly nausea and vomiting. Decreasing renal function resulted in increasing AEs and subjects in CVT 3036 with creatinine clearance ≤ 30 mL/min were noted to have an increased risk of nausea, dizziness, hypotension, and more notably also of cardiac failure, dyspnoea and myocardial infarction. While aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal (ULN) did not increase AE incidence, significant hepatic impairment was an exclusion criteria from the trials. There

were no evident safety concerns in other subgroups of CHF, presenting syndrome, ST segment depression, TIMI score, asthma, chronic obstructive pulmonary disease (COPD), low blood pressure and/or low heart rate and/or prolonged atrioventricular (AV) conduction.

Taking concomitant diltiazem or verapamil mildly increased the risk of AEs, particularly of dizziness. Post-marketing data has found a risk of musculoskeletal AE and rhabdomyolysis with concomitant simvastatin use. The PI states that the dose of simvastatin used concomitantly with ranolazine should be limited to 20 mg once daily.

Ranolazine has been on the US market since 2006 and EU since mid-2008 and an estimated 560,000 patients have been exposed in the US. Post-marketing data review has resulted in the addition of dysuria, urinary retention, coordination abnormal, gait disturbance hallucination, confusional state, headache, syncope, tremor, paraesthesia, hypoesthesia, angioedema, rash and pruritus in the CCDS. Further risks have been highlighted regarding the need for dose adjustment of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range when co-administered with ranolazine. A review on the risk of TdP and VT to July 2010 found no additional risks necessitating change to the CCDS. As this review is 5 years old it should be updated.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ranolazine in the proposed usage are:

- Anti-ischaemic and anti-anginal efficacy in stable angina as measured by exercise duration, reduction in angina attacks and nitroglycerin consumption. The benefit is modest with approximately 24 seconds improvement in exercise duration after 12 weeks of treatment with ranolazine 750 mg BD and reduction of less than one angina attack per week.
- Tolerance did not develop after 12 weeks of treatment and rebound in angina (as measured by exercise duration) was not observed on cessation of treatment.
- In chronic angina patients with acute coronary syndrome (non-ST segment elevation), a benefit on exercise duration and quality of life (QOL) was seen. However, ranolazine showed no benefit in improving cardiovascular outcomes in patients presenting with non-ST elevation acute coronary syndrome.
- Efficacy was consistent across age subgroups, while data in females is less convincing than in males.
- A large safety database with sufficient treatment duration and covering a broad patient population.
- A lack of haemodynamic effects.
- A lower risk of clinically significant arrhythmias on 7 days of Holter monitoring in non-ST elevation ACS patients.

First round assessment of risks

The risks of ranolazine in the proposed usage are:

- Frequent adverse events of constipation, nausea, dizziness, vomiting and headache.

- Dose dependent increase in risk of AEs. The 1,500 mg BD dose is poorly tolerated and at high exposure there was the risk of syncope, confusion, lethargy, hypotension, blurred vision and diplopia.
- A low safety margin between clinical doses (particularly 1,000 mg BD) and intolerable side effects.
- Dose dependent QTc interval prolongation which has been well characterised. Reassuringly, there was no increased risk of mortality, sudden death or arrhythmias. The QT prolongation risk increases in hepatic impairment.
- Complex pharmacokinetics with metabolism via CYP3A4 and CYP2D6.
- High risk of drug-drug interactions.
- Many factors leading to increased plasma ranolazine concentrations including renal impairment, hepatic impairment, low body weight, elderly, class III/IV CHF, concomitant CYP3A4 or P-gp inhibitors and poor metabolisers of CYP2D6.
- Efficacy and safety data in non-Caucasians were limited.
- Insufficient efficacy data for use as monotherapy.

First round assessment of benefit-risk balance

The aim of treatment in coronary artery disease is to improve prognosis through prevention of MI and death and to minimise or abolish symptoms through lifestyle changes, medications and revascularisation (European Society of Cardiology 2006). The typical agents used for symptomatic treatment in stable angina are nitrates, beta blockers and calcium channel blockers. The European Society of Cardiology recommends that dosing with one agent is optimised prior to initialising treatment with a second. While numerous long standing therapies currently exist, the possibility of contraindications, side effects or insufficient efficacy means there is still a clinical place for newer anti-anginal therapies.

There are three classes of anti-ischaemic drugs commonly used in the management of angina pectoris: beta blockers, calcium channel blockers and nitrates. Beta blockers relieve symptoms by reducing both heart rate and contractility; calcium channel blockers improve symptoms by causing coronary and peripheral vasodilatation and reducing contractility while nitrates decrease myocardial oxygen demand via vasodilatation which is predominantly systemic.

Ranolazine is a novel small molecule of a new pharmacological class which is believed to have its anti-ischaemic and anti-anginal effects via inhibition of the late sodium current in cardiac cells with a resultant reduction of intracellular sodium and intracellular calcium overload. The calcium overload during myocardial ischaemia is said to contribute to impaired left ventricular relaxation and diastolic compliance and this leads to further reduction in myocardial perfusion. Ranolazine's anti-anginal effects come from reducing these intracellular ionic imbalances during ischaemia. This mechanism of action is different from current anti-anginals which act through vasodilation or reductions in heart rate or blood pressure.

The clinical trial data in the dossier provided sufficient evidence of clinically relevant, albeit modest, efficacy to support treatment of chronic stable angina. The pivotal trial (CVT 3033) met the guideline recommendations for investigation of a product in stable angina pectoris.[26] Its primary endpoint of exercise capacity was positive, supported by secondary endpoints and also data from Study CVT 3037 which assessed angina attacks and NTG consumption. In addition, although there was a lack of benefit in non-ST elevation ACS (no improvement in the primary outcome measure of cardiovascular death,

MI or recurrent ischaemia), the post-hoc analysis of a subgroup of patients with chronic angina showed an ETT improvement similar to other studies and so provided valuable supportive evidence.

CVT 3033 assessed ranolazine on top of atenolol, diltiazem or amlodipine, and in CVT 3037 treatment was on top of amlodipine. Therefore data support the use of ranolazine as an add-on therapy in chronic angina. There is insufficient evidence for ranolazine's use as monotherapy as this regimen was only used in one dose ranging, crossover trial of short duration (CVT 3031). In contrast to the previous application, the sponsor now proposes an indication for patients "who are inadequately controlled or intolerant to first line anti-anginal therapies". This is acceptable and is now in line with that approved in the EU.

The lack of haemodynamic effects is a noteworthy positive for the safety profile of ranolazine. On the other hand, ranolazine has a number of significant safety concerns. These include a dose dependent prolongation of the QT interval, complex pharmacokinetics, a high risk of drug-drug interactions, a low safety margin and many factors which lead to increased levels (such as renal impairment, hepatic impairment, low body weight and increased age).

While the cardiovascular outcome study was negative, for a drug which prolongs the QT interval it was reassuring that this large trial demonstrated no increased risk of sudden death or arrhythmias.

In the clinical setting, the target population is very likely to have comorbidities, be on multiple medications, or be more fragile than those included in the clinical trials. Consequently, there is a significant risk of adverse effects related to increased exposure and it will be essential that such risks are strategically managed.

As stated in the previous evaluation, it appears from Study CVT 3036 that the 1,000 mg dose was tolerated. Nonetheless, this dose may not be safe in populations at risk of increased exposure, particularly outside the clinical trial setting. Given Study CVT 3033 found similar efficacy with the 750 mg dose, with a lower AE rate compared to the 1,000 mg dose, it was concluded that 750 mg BD should be the next step in up-titration from 500 mg BD. The sponsor has since adopted this recommendation and limited the maximum dose at 750 mg BD. While it is acknowledged that the 375 mg BD dose may not be efficacious, to ensure cautious dose titration, starting with this lower dose is the prudent course of action and the evaluator agrees with these revised dosing proposals.

Dosing instructions, contraindications, precautions and drug-drug interactions need to be clearly provided and assessed. The evaluator therefore recommends that there is specific action taken, not only for medical professionals and pharmacists, but also for patients which clearly appraises them of all relevant details. In the EU there is a Patient Alert Card which informs patients about the main interactions, contraindications and precautions of ranolazine. The sponsor states that this is not proposed in Australia. The evaluator believes that this would be beneficial in our setting and so it, or something similar, should be implemented.

There is a clinical need for anti-anginal therapy for certain patients who may have ongoing symptoms despite optimised therapy or who may be intolerant to current treatments. Ranolazine is found to have positive efficacy data as an add-on therapy for chronic stable angina, however this comes with considerable safety risks. To a large extent these risks can be managed by lowering the starting dose, cautious dose titration, limiting the maximum recommended dose, excluding populations at high risk, clear labelling regarding other at risk patient groups and thorough education of doctors, pharmacists and patients. Given these facts, the novel mechanism of action and the clinical need, the evaluator finds the benefit-risk balance of ranolazine, given the proposed usage, is favourable. This recommendation is subject provision of further post-marketing data, including that

relating to ventricular tachycardia and torsade de pointes, further clarification on efficacy in females and satisfactory responses to the other questions and comments.

First round recommendation regarding authorisation

It is recommended that ranolazine 375 mg, 500 mg and 750 mg prolonged release tablets are approved for the proposed indication:

> *Ranexa 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 anti-anginal therapies (such as beta-blockers and/or calcium antagonists).*

This recommendation is subject to:

- Satisfactory responses to the questions and comments including those relating to the PI and CMI.
- Assessment of up to date post-marketing pharmacovigilance data including a review of the risk of torsade de pointes and ventricular tachycardia.
- A risk management plan that is more proactive than routine pharmacovigilance and that includes specific information for doctors, pharmacists and patients on the contraindications, precautions and interactions of ranolazine.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the clinical questions the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ranolazine in the proposed usage are unchanged from those identified in the first round benefit-risk assessment.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ranolazine in the proposed usage are unchanged from those identified in the first round benefit-risk assessment.

Second round assessment of benefit-risk balance

A more recent PSUR (covering the period of January 2013 to January 2015) was provided which included post-marketing data on torsade de pointes and ventricular tachycardia. These data did not indicate any risks above those already outlined in the PI.

Most comments on the PI have been satisfactorily addressed. There remain a few outstanding issues. The first relates to efficacy in women compared to men. The presented trial data in the proposed population of chronic angina pointed towards lower efficacy in women. It is acknowledged that there may be issues with the use of the ETT as an efficacy outcome measure in women and that the cardiovascular outcome Study CVT 3036 provided data pointing towards no reduced benefit in females on the rate of recurrent

ischaemia. Nonetheless, for reasons discussed in the evaluation of the sponsors response to issues raised, the evaluator has not seen sufficient evidence to refute the fact that women with chronic angina may not respond as well to ranolazine. This fact still needs inclusion in the PI.

Overall, the presented data have not altered the benefit-risk balance for ranolazine, given the proposed usage, which is favourable. This is subject to final changes being made to the PI and CMI. It is also still recommended that the risk management plan is more proactive than routine pharmacovigilance and that it includes specific information for doctors, pharmacists and patients on the contraindications, precautions and interactions of ranolazine

Second round recommendation regarding authorisation

It is recommended that ranolazine 375 mg, 500 mg and 750 mg modified release tablets are approved for the proposed indication:

> *Ranexa 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 anti-anginal therapies (such as beta-blockers and/or calcium antagonists).*

This recommendation is subject to:

- Satisfactory responses to the comments relating to the PI and CMI.
- A risk management plan that is more proactive than routine pharmacovigilance and that includes specific information for doctors, pharmacists and patients on the contraindications, precautions and interactions of ranolazine.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 7.2 (dated 6 March 2013, DLP 26 July 2011) and Australian Specific Annex Version 1.1 (dated 8 May 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 19.

Table 19: Summary of ongoing safety concerns

Summary of ongoing safety concerns	
Important identified risks	Constipation, nausea, vomiting Dizziness, syncope Confusion, hallucinations Hypotension QT prolongation Angioderma Drug-drug interaction with sensitive

Summary of ongoing safety concerns	
	CYP3A4 statins (simvastatin, lovastatin) to increase the plasma concentrations and the toxicity of these drugs Drug-drug interactions with immunosuppressants with a narrow therapeutic index metabolised by CYP3A4 (ciclosporin, tacrolimus, sirolimus, everolimus)
Important potential risk	Drug-drug interaction with metformin
Important missing information	Effects on male infertility Use in pregnant or lactating women and the paediatric population Ethnicity other than Caucasian safety information for patients with moderate and severe hepatic impairment Safety information for patients with severe end stage renal disease requiring dialysis Drug-drug interactions with Class Ia and Class III antiarrhythmics except amiodarone Antihistamine (for example terfenadome, astemizole, mizolastine), certain antiarrhythmics (for example quinidine, disopyramide, procainamide), erythromycin and tricyclic depressants (for example . 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 (for example tricyclic antidepressants and antipsychotics)

Pharmacovigilance plan

The sponsor proposed the following routine pharmacovigilance[28] plan for the identified/potential risks and missing information presented in Table 20.

Table 20: Proposed pharmacovigilance for specific safety concerns

Safety concern	Planned action(s)
Constipation, nausea, vomiting	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications. -wording in the Patient Alert Card
Dizziness, syncope	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications. -wording in the Patient Alert Card
Confusion, hallucination	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications.
Hypotension	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications.
QT prolongation	-routine pharmacovigilance -special form to follow-up cases -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications. -wording in the Patient Alert Card
Angioedema	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications.

[28] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Safety concern	Planned action(s)
Drug-drug interaction with statins which are sensitive to CYP3A4 inhibition (simvastatin, lovastatin)	-routine pharmacovigilance -an evaluation of new case reports of and a cumulative summary of possible interactions with statins will be provided in each PSUR. -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications. -wording in the Patient Alert Card
Drug-drug interaction with immunosuppressants with a narrow therapeutic index metabolised by CYP3A4 (ciclosporin, tacrolimus, sirolimus, everolimus)	-routine pharmacovigilance -special form to follow-up cases -IMS Disease Analyzer data will be collected for the analysis of medical history/other disease sate and concomitant medications. -wording in the Patient Alert Card
Drug-drug PK interaction between ranolazine and metformin	-routine pharmacovigilance
Male infertility	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information
Use in pregnant or lactating women and the paediatric population	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information
Ethnicity other than Caucasian	-routine pharmacovigilance: If ethnicity data is volunteered, these data will be collected and included in the individual case reports and PSURs
Safety information for patients with moderate or severe hepatic impairment	-routine pharmacovigilance
Safety information for patients with severe and end-stage renal disease requiring dialysis	-routine pharmacovigilance
Drug-drug interactions with Class Ia and Class III antiarrhythmics except amiodarone	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information -wording in the Patient Alert Card
Antihistamines (for example terfenadine, astemizole, mizolastine), certain antiarrhythmics (for example quinidine, disopyramide, procainamide), erythromycin,	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information -wording in the Patient Alert Card

Safety concern	Planned action(s)
and tricyclic antidepressants (for example imipramine, doxepin, amitriptyline)	
Real-world safety information for drug-drug interactions with potent CYP3A4 inhibitors which may cause ranolazine plasma concentration increases	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information -wording in the Patient Alert Card
Drug-drug interactions with CYP2D6 substrates which may need to be down-titrated (tricyclic antidepressants and antipsychotics)	-routine pharmacovigilance -IMS Disease Analyzer data will be collected for identifying this missing information -wording in the Patient Alert Card

Risk minimisation activities

The sponsor proposes routine risk minimisation activities (for example PI labelling) for all identified/potential safety concerns and missing information.[29]

Risk minimisation plan

The sponsor advises in the ASA (version 1.1, 8 May 2015) that no additional risk minimisation activities are proposed for Australia.

Reconciliation of issues outlined in the RMP report

Table 21 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 21: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Concomitant administration of Ranexa with CYP3A4 inducers is contraindicated. This is further supported by advice in the PI indicating that co-administration with CYP3A4 inducers, is expected to lead to lack of efficacy. 'Drug interactions with CYP3A4 inducers' should be included as an important identified risk in the Summary of Safety	The sponsor acknowledges the comment and confirms that the drug interactions with CYP3A4 inducers are already included in the submitted European RMP in section "Identified and Potential Interactions". However, according to the current good pharmacovigilance practices (GVP) (module V), the definition of an important identified risk is a risk "that could have an impact on the risk-benefit balance of the product or have implication for public	The sponsor's response is noted and is considered acceptable from a RMP perspective.

[29] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Concerns.	health" and the lack of drug effect would not fit in this definition. Therefore the sponsor does not agree to include this risk in the summary of safety concerns section.	
There are Precautions in the PI relating to the use of Ranexa concomitantly with P-gp inhibitors. 'Drug interactions with P-gp inhibitors' should be included as an important identified risk in the Summary of Safety Concerns.	The sponsor acknowledges the comment and confirms that the drug interactions with P-gp inhibitors' are already included in the submitted European RMP in section "Identified and Potential Interactions". The risk associated to the drug interactions of Ranexa with P-gp inhibitors is the increase plasma concentrations of ranolazine leading potentially to Ranexa overdose with a potential increase incidence of dizziness, nausea and vomiting. In addition, diplopia, lethargy and syncope were observed in an intravenous overdose study in healthy volunteers (see proposed PI). The overdose itself seems to be not in line with the Important Identified Risk definition according to the current GVP and its potential effects are already well addressed in the summary of safety concerns.	The sponsor's response is noted and is considered acceptable from a RMP perspective.
There are Precautions relating to the use of Ranexa by patients of low weight (≤ 60 kg) and by patients with moderate to severe CHF (NYHA Class III-IV). Use in these patient groups should be included as important potential risks in the summary of safety concerns.	This safety issue is well addressed in the proposed PI. The use of Ranexa in this population could lead to Ranexa over exposure. This in itself does not appear to be a risk in line with the definition of "important identified risks" (see response above) and whose potential effects are already well addressed in the RMP summary of safety concerns.	The sponsor's response is noted and is considered acceptable from a RMP perspective.
The summary of safety concerns identifies drug-drug interactions with CYP2D6 substrates as Missing Information. The PI extends CYP2D6 Precautions here relating to increased exposure risk in higher-risk patients lacking CYP2D6	The sponsor acknowledges the comment and confirms that drug-drug interactions with CYP2D6 substrates, has been discussed in the latest PSUR April2015 recently assessed by EMA. We confirm that this interaction is described either in the sections 4.2 and 5.2 of the EU-SmPC and among the Identified	The sponsor's response is noted and is considered acceptable from a RMP perspective. However, it is noted that the sponsor should provide a copy of PSUR April2015 for

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
activity (that is poor metabolisers). This is clinically different and this should be included in the summary of safety concerns.	and Potential Interaction of the submitted EU-RMP. The information reported in the abovementioned documents is consistent, even if no specific information is available on the concomitant use of ranolazine with CYP2D6 substrates (missing information). On the basis of the product pharmacokinetics, a risk of ranolazine overexposure is expected in patients lacking CYP2D6 activity (that is poor metabolisers), so specific precautions are reported in the proposed PI as in the EU SmPC. No changes to the summary of safety concerns of the ASA are therefore considered necessary.	consideration by the TGA.
General gastrointestinal effects are noted for Ranexa (constipation, nausea, and vomiting). It is recommended that the sponsor provide more information or analysis on the rare, more serious, adverse gastrointestinal events of pancreatitis and erosive duodenitis reported in the Phase III angina studies, and consider whether these more serious effects should be included in the summary of safety concerns.	The sponsor acknowledges the comment and confirms that pancreatitis and erosive duodenitis are reported in Section 4.8 of EU-SmPC and of the proposed PI with rare frequency. Post-marketing data are in line with these results. In fact, in the cumulative post-marketing experience, only 6 cases of pancreatitis, 1 case of acute pancreatitis and 2 cases of duodenitis (no erosive duodenitis) have been collected (data up to 26 January 2015) over a cumulative exposure of about 16.5 million of patients all over the world. On the basis of this information, we do not believe that the inclusion of the risk in the summary of safety concerns is required.	The sponsor's response is noted and is considered acceptable from a RMP perspective. However, it is noted that the sponsor should provide a copy of PSUR April 2015 for consideration by the TGA.
It is noted that the sponsor has grouped several adverse effects together in the Summary of Safety Concerns, that is 'constipation, nausea, vomiting', 'dizziness, syncope', and 'confusion, hallucinations'. The sponsor should provide justification as to why these distinct	The sponsor acknowledges the comment and confirms that these AEs were analysed together since they were considered part of the same pathological condition. However, according to PRAC assessment (EMA/PRAC/543523/2013) on the European Risk Management Plan (EU-RMP) Version 7.2, these topics have been removed as Important	The sponsor's response is noted and is considered acceptable from a RMP perspective. However, it is noted that the sponsor should provide a copy of PSUR April 2015for consideration by the TGA.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
adverse effects are grouped. It is expected in future reporting (PSURs) that these adverse effects will be addressed separately for clarity.	Identified Risks and are not discussed further in the latest PSUR/PBRER (see page 73 of PSUR-Apr-2015- 16.3.2; New Information on Important Identified Risks; Table 16-2; Deleted Important Identified Risks).	Further, the sponsor has advised that following PRAC assessment of EU-RMP Version 7.2, these adverse effects were removed as Important Identified Risks. In this regard, the RMP/ASA should be updated to reflect this, and the updated materials provided to the TGA.
With regards to pharmacovigilance, it is advised by the sponsor in the EU-RMP that prescribing patterns, pertinent patient demographic data and concomitant medications would be evaluated via an IMS Disease Analyzer drug utilisation study ('Ranolazine IMS Disease Analyzer Study MEN-RAN-303-IMS.001). The sponsor advised in the EU-RMP that the planned date for submission of the final data for this study was 2 April 2013, along with PSUR 8. These reports, as available, should be provided to the TGA for consideration.	The sponsor acknowledges the comment and confirms that the requested data can be found in the latest PSUR update (PSUR April 2015) refer to Section 8 "findings from non-interventional studies-8.1.3. MEN-RAN-303-IMS.001" (pages 32-34).	The sponsor should provide a copy of PSUR April 2015 for consideration by the TGA.
It is noted that the SPC contains the information regarding increased adverse events in the elderly, patients with renal impairment, and patients with low body weight in the Undesirable Effects section. This information is included in the Clinical Trials section of the PI; however, the sponsor should also include reference to such in the Adverse Effects section of the PI (or make reference to 'see Clinical Trials section' in the Adverse Effects section	The sponsor acknowledges the comment and submits the PI revised according to the TGA's indications.	The sponsor's response is noted. Changes to the PI are reserved for final determination by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
of the PI). Relevant text includes: Elderly, renal impairment and low weight: In general, adverse events occurred more frequently among elderly patients and patients with renal impairment; however, the types of events in these subgroups were similar to those observed in the general population. Of the most commonly reported, the following events occurred more often with Ranexa (placebo corrected frequencies) in elderly (≥ 75 years of age) than younger patients (< 75 years of age): constipation (8% versus 5%), nausea (6% versus 3%), hypotension (5% versus 1%), and vomiting (4% versus 1%). In patients with mild or moderate renal impairment (creatinine clearance ≥ 30 to 80 ml/min) compared to those with normal renal function (creatinine clearance > 80 ml/min), the most commonly reported events and their placebo corrected frequencies included: constipation (8% versus 4%), dizziness (7% versus 5%), and nausea (4% versus 2%). In general, the type and frequency of adverse events reported in patients with low body weight (≤ 60 kg) were similar to those of patients with higher weight (> 60 kg); however, the placebo-corrected frequencies of the following common adverse events were higher in low body weight than heavier patients: nausea (14%		

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).		
The following is noted in the sponsor's justification for not employing a patient alert card (PAC) in Australia: A preliminary assessment of the local Australian market has shown that current standard practices encompass these activities more suitably (at the point of prescribing as well as at point of dispensing). For example, safety alerts for drug interactions are integrated into the prescribing software for doctors and "alerts" do prompt the prescribing physician to take appropriate action. If this type of safety alert is proposed as a risk minimisation strategy, the sponsor should provide more details regarding their intent to incorporate alerts relating to drug interactions with ranolazine.	The sponsor acknowledges the comment and confirms that there are multiple software providers with different types of applications which include electronic medical records and prescribing for prescribers and dispensing for pharmacists. These applications provide a range of functionality for the user including full product information and consumer medicine information, which are either manually loaded into the application or loaded directly from eMIMs on monthly basis, and automated alerts for drug interactions based on the PI. For example, dispensing software provider FRED, automatically have an alert if there is a drug interaction detected from the patient's history during dispensing (see image of the alert from FRED included in the response).	The sponsor's response is noted. However, it remains that a patient-specific activity be implemented to mitigate the risks associated with drug interactions.
As a risk minimisation tool a PAC serves to facilitate communication between the consumer and health care providers other than the prescribing doctor. This may be significant for patients being administered Ranexa given the potential for specialist treatment of co-morbidities. Given the sponsor does not intend to issue a PAC in Australia the sponsor should propose what would replace this mechanism in the Australian context.	The sponsor acknowledges the comment and confirms the following. PACs are not, and have not been a common or familiar tool for the Australian patient population. An initial assessment of the Australian market has shown that no other product relies on PACs as a facilitator between the consumer and health care provider. Other cardiovascular products, including warfarin which has significant drug-drug interactions with other medicines and safety implications with the INR/ PT time, has no PAC. We propose to make the information included in the PAC	The sponsor's response is noted. The response highlights that patient-specific information (that is CMI) will be included in the packaging of all products. However, it remains that additional patient-specific education could be implemented to further mitigate the risks associated with drug interactions. Regarding the CMI, changes to the CMI are reserved for final determination by the

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	more prominent in the CMI by way of a call-out box, similar to the call out box for dosing in the current Abstral CMI. It is Menarini's standard policy to enclose a printed leaflet (CMI) within the packaging of all Menarini products in addition to the electronic distribution by pharmacists and availability of the CMI on the Menarini Australia website (www.menarini.com.au).	Delegate.

Summary of recommendations

Suggested wording for conditions of registration

RMP

At this time, wording for the RMP conditions of registration cannot be advised. The sponsor is requested to provide comment on the implementation of additional patient education regarding the risk of drug interactions.

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

Angina occurs when myocardial oxygen demand exceeds supply. Demand is typically increased by exercise (especially isometric) or emotion. Supply is restricted by atherosclerotic obstruction of the coronary arteries and anaemia. The pain of stable angina is typically transient, lasting less than 10 minutes, and subsides promptly with rest. The pain usually bears a predictable relationship to walking and other activities involving physical effort or emotional stress. The aims of continuing therapy to prevent symptoms of angina are to reduce myocardial oxygen demand and increase oxygen supply, increase effort tolerance, and prevent the development of symptoms and complications.

The usual treatments include beta-blockers (atenolol or metoprolol), non-dihydropyridine calcium channel blockers (diltiazem, verapamil) which reduce heart rate and can be used as an alternative to a beta blocker if the patient has a contraindication to beta blockade. Dihydropyridine calcium channel blockers (amlodipine and controlled-release nifedipine) can be used as monotherapy or added to beta-blocker therapy but these drugs may increase the heart rate. For patients who are in sinus rhythm but whose symptoms are not controlled and who are intolerant of other drugs (for example beta blockers, verapamil or diltiazem), ivabradine, which reduces heart rate may be given. Ivabradine, the most recently approved medicine for the management of stable angina was registered in 2006. Long-acting nitrates provide symptomatic relief of angina however tolerance to all forms of nitrate therapy develops rapidly.

Ranolazine is a novel small molecule of a new pharmacological class which is believed to have its anti-ischaemic and antianginal effects via inhibition of the late sodium current in cardiac cells with a resultant reduction of intracellular sodium and intracellular calcium overload. The clinical development programme for ranolazine commenced in 1985 with initial studies of intravenous (IV) and immediate release (IR) formulations. In order to maintain an effective plasma concentration, an extended release (ER) formulation was developed. There have been sponsorship and formulation changes subsequently. A prolonged release (PR) formulation has been proposed for registration.

In 2009, Gilead Sciences submitted an application to register ranolazine (PM-2009-03573-3-3). That submission sought the registration of 500 mg and 1000 mg prolonged release tablets and the proposed indication was for the treatment of chronic angina. The clinical evaluator of that submission considered the benefit-risk balance was negative for use of ranolazine as first-line, monotherapy treatment and that its use should be restricted to add-on therapy. That evaluator also recommended that the 750 mg BD dose be made available and questioned the safety of the 1000 mg dose in populations at risk of increased exposure. That submission was withdrawn by Gilead in mid-2011. The reason provided to the TGA for withdrawal was "Unable to provide a full and complete response in the timeframe required, in relation to the impurity method and method validation". The dossier for the current submission is applying for a different range of strengths (375 mg, 500 mg and 750 mg tablets) and a different indication in chronic angina (add-on or second line therapy). The tradename and formulations of the 500 mg tablets are identical to the previous submission although tablet markings differ.

Ranexa (375 mg, 500 mg and 750 mg PR tablets) was approved in the EU in 2008. The indication there is the same as has been proposed in Australia. Ranexa is under evaluation in NZ (2014) and approved in Singapore (2015) with the same indication.

The sponsor stated that the data set is essentially the same as that submitted in the EU except that in Australia additional data have been submitted to address previous TGA queries for example DMA impurity toxicological assessment, new HPLC impurity method and validation.

Ranexa as 500 mg and 1000 mg prolonged release tablets was granted marketing authorisation in the USA in 2006. The indication in the USA is:

> *Ranexa is indicated for the treatment of chronic angina.*
>
> *Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid-lowering therapy, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.*

When first marketed in 2006 the indication was:

> *Ranexa is indicated for the treatment of chronic angina. Because Ranexa prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs. Ranexa should be used in combination with amlodipine, beta-blockers or nitrates. The effect on angina rate or exercise tolerance appeared to be smaller in women than men.*

Quality

There are no quality or biopharmaceutic issues that would preclude registration of ranolazine. The presence of the genotoxic impurity 2,6-dimethylaniline (DMA) had caused serious concern. The company subsequently agreed to revise the finished product specifications to include a test and limit for the degradant DMA. These limits have been accepted by the chemistry evaluator (≤ 4 ppm at release and ≤ 12 ppm at shelf life limit with release testing of one batch every 6 months).

The drug substance contains a single chiral centre and is presented as the racemate. Four potential organic impurities have been identified for which appropriate limits are included in the drug substance specifications. The proposed drug substance specifications are considered adequate to ensure the quality and consistency of the manufacture of the finished product.

In this submission the company has included justifications addressing deficiencies in the previous Ranexa submission. The chemistry evaluator noted that as ranolazine has a relatively short elimination half-life of 2 hours it has been formulated for sustained release. The proposed release mechanism of the tablets is unusual in using a pH sensitive methyl- and ethyl- acrylate copolymer as matrix combined with hypromellose as tablet binder which also retards release.

The extended release properties of the tablets are imparted by the excipients methacrylic acid-ethyl acrylate copolymer 1:1 and hypromellose. On contact with water these form a polymeric matrix through which water must diffuse to dissolve and release the drug substance. The solubility of this matrix is pH dependent; being insoluble at low pH and soluble above pH 5. Thus in relation to dissolution, there are two competing factors: the solubility of the drug substance decreases as pH increases and the release rate from the polymeric matrix increases as the pH increases. Thus as pH increases from the pH 1.2 to pH 7, the dissolution rate decreases and then increases again to higher than at pH 1.2. This effect of pH may affect the bioavailability for achlorohydric patients (although data suggests that a modest (approximately 5%) slowing of dissolution rate at the 4 hour test point won't significantly affect the bioavailability).

The chemistry evaluator accepted that the tablets used in the Phase III clinical trials were effectively bioequivalent to the commercial tablets.

Nonclinical

The nonclinical evaluator had not provided a recommendation on approval of ranolazine due to the presence of 2,6-dimethylaniline (DMA). Satisfactory limits for that impurity/ degradant have now been agreed.

The nonclinical data set for this re-submission was generally the same as that previously provided, with the exception of a new in vitro study concerning the effects on uptake and efflux transporters (Study AD-259-2005). As well, the sponsor provided two toxicological risk assessment reports to justify the presence of 2,6–dimethyl aniline as a non-specified impurity. In the previous application, an outstanding issue concerned the presence of the unspecified process and degradation impurity 2,6-dimethylaniline (DMA also known as 2,6-xylidine) in drug product. DMA is a known mutagen and the IARC categorises it as a Class 1 carcinogen (mutagenic impurity with positive carcinogenicity data).

The nonclinical evaluator noted that although the sponsor did not conduct any further investigations on DMA, the commissioned risk assessments provided adequate assurances that potential exposure to DMA is negligible when used at release and will be unlikely to pose a significant risk of carcinogenicity when used at release levels. However, as it is clear that DMA levels increase over time and the specifications are somewhat ambiguous on whether non-specified degradation impurities include DMA, the sponsor should ensure that the shelf life for Ranexa is kept to 24 months or lower to minimise the potential exposure to DMA through degradation.

The nonclinical evaluator of the previous submission (PM-2009-03573-3-3) noted that The mechanism of action of ranolazine is largely unknown. Pharmacological data suggested that it inhibited the late inward sodium current (INa) with higher potency than flecainide and dofetilide, reduced myocardial $[Ca^{2+}]i$ overload, and had anti-ischaemic efficacy independent of any effects on HR, arterial BP, left ventricular contractility, or

systemic vascular resistance. Receptor binding screens showed that ranolazine and its R- and S-enantiomers had moderate affinity for α1-adrenergic receptors, β1-adrenergic receptors, β2-adrenergic receptors, and serotonin 5-HT1A and 5-HT2 receptors, but whether blockade of such receptors contributes to the overall clinical pharmacology profile is unclear.

Ranolazine had negative inotropic effects and anti-arrhythmic activity, and did not appear to have torsadogenic potential despite its inhibition of IKs and IKr and its moderate prolongation of QT interval. Few detrimental effects of ranolazine were seen at plasma concentrations within the expected therapeutic range (≤ 10 μM).

The weight of evidence suggests that ranolazine is not genotoxic and does not have primary carcinogenic potential. However, studies in a specific type of transgenic rat suggested that ranolazine may have some tumour promoting potential. While the clinical relevance of these findings is unclear, they should be noted in the PI in the Carcinogenicity section.

Clinical

Pharmacokinetics

Ranolazine (RAN) is a racemate that consists of a 1:1 ratio of (R) and (S) enantiomers. The PK of each racemate was examined in a single dose study of an IR formulation and there were no significant differences in the PK parameters between the (+) and (-) enantiomers. There was no evidence of inter-conversion of the enantiomers.

Absolute bioavailability of the ER formulation has not been directly examined, however after oral administration of ^{14}C-ranolazine as a solution, 73% of the dose was systemically available as ranolazine or metabolites. The rate of absorption is highly variable. For the ER formulation T_{max} ranged from 2 to 18 h with a mean of 6 h. Following 6 days of dosing with 500 mg ranolazine ER BD the mean C_{max}, AUC_{0-12}, T_{max} and t½ were 1,770 ng/mL, 13,700 ng.h/mL, 3.85 hours and 6.82 hours, respectively.

Across studies the effective terminal elimination half-life for the ER formulation is 4 to 5 hours, on average compared with 1.50 to 1.58 hours for ranolazine given intravenously. This longer apparent elimination half-life indicates that with the ER formulation drug absorption is ongoing beyond 12 hours. Within a dose range of 500 to 1000 mg BD, the peak/trough ratio of the ranolazine plasma concentration is 1.6 to 3.0. With multiple dosing of the ER formulation of up to 1500 mg BD, steady state is achieved within 6 days. Mean apparent Vd is 53.2L. Total protein binding of ranolazine is 61 to 64% over the concentration range 250 to 10,000 ng/mL.

Pharmacokinetics are approximately linear within the proposed dose range in single dose studies but ranolazine AUC_{τ} and C_{max} at steady state increase more than proportionally to dose, consistent with parallel linear and saturable elimination. Food did not significantly affect the AUC or C_{max} of ranolazine PR.

Ranolazine is extensively metabolised with approximately 3% excreted unchanged. Multiple metabolic pathways were identified in a radio-label study with 4 major metabolites. Ranolazine is primarily metabolised by CYP3A4 and to a lesser extent CYP2D6. Ranolazine and RS-88390, a metabolite of ranolazine, inhibit CYP3A4. The activity of the major metabolites has not been determined. The PK of 12 metabolites for the ranolazine dose range 500 mg BD to 1,500 mg BD are shown in Table 22.

Table 22: CVT 3015 Summary of Mean steady state (Day 6) Pharmacokinetic parameters of ranolazine metabolites following multiple oral doses of ranolazine PR (500, 1,000, 1,500 mg BD) to healthy subjects (Study CVT 3015)

Ranolazine/Metabolite	Parameter	Dose		
		500 mg bid	1000 mg bid	1500 mg bid
Ranolazine	N	13	14	14
	AUC_{0-12} (ng•h/mL)	13,700	32,900	56,100
	C_{max} (ng/mL)	1,770	3,830	6,220
	$t_{½}$ (h)	6.82	6.65	7.34
CVT-2512 (RS-88640)	N	13	13	13
	AUC_{0-12} (ng•h/mL)	1,600	2,386	2,738
	C_{max} (ng/mL)	160	231	275
	$t_{½}$ (h)	21.04	24.43	27.45
CVT-2514 (RS-88390)	N	13	13	13
	AUC_{0-12} (ng•h/mL)	4,528	8,869	11,590
	C_{max} (ng/mL)	498	913	1,170
	$t_{½}$ (h)	10.04	11.99	15.83
CVT-2738 (RS-94287)	N	13	13	13
	AUC_{0-12} (ng•h/mL)	3712	8044	13870
	C_{max} (ng/mL)	377	770	1295
	$t_{½}$ (h)	9.58	10.09	10.80
RS-89289	N	13	13	13
	AUC_{0-12} (ng•h/mL)	349	690	1,032
	C_{max} (ng/mL)	38.3	73.5	104
	$t_{½}$ (h)	15.3	15.7	17.5
CVT-4786	N	13	13	13
	AUC_{0-12} (ng•h/mL)	2,944	6,555	10,310
	C_{max} (ng/mL)	400	814	1,127
	$t_{½}$ (h)	6.65	6.01	7.73
RS-88681	N	13	13	13
	AUC_{0-12} (ng•h/mL)	436	938	1,454
	C_{max} (ng/mL)	43.0	89.5	135
	$t_{½}$ (h)	13.3	12.7	14.3
RS-89983	N	13	13	13
	AUC_{0-12} (ng•h/mL)	310	614	973
	C_{max} (ng/mL)	32.2	61.4	94.7
	$t_{½}$ (h)	10.5	10.4	12.8
RS-89961	N	13	13	13
	AUC_{0-12} (ng•h/mL)	908	2,550	4,882
	C_{max} (ng/mL)	112	275	500
	$t_{½}$ (h)	6.86	5.80	6.78
RS-88597	N	13	13	13
	AUC_{0-12} (ng•h/mL)	683	1,762	2,898
	C_{max} (ng/mL)	86.4	203	319
	$t_{½}$ (h)	8.12	9.16	12.7
RS-101647	N	13	13	13
	AUC_{0-12} (ng•h/mL)	544	1,149	1,714
	C_{max} (ng/mL)	55.6	110	166
	$t_{½}$ (h)	13.5	13.6	17.2
RS-88772 & RS-88835	N	13	13	13
	AUC_{0-12} (ng•h/mL)	510	1,197	2,212
	C_{max} (ng/mL)	59.8	133	231
	$t_{½}$ (h)	7.86	9.43	11.3

Mild renal impairment increased the C_{max} and AUC of ranolazine by 1.58 and 1.75 fold, respectively and these increases were maintained in subjects with moderate renal impairment and were further enhanced in subjects with severe renal impairment. Table 23 shows the PK of ranolazine and 12 of its metabolites in subjects with renal impairment and healthy controls. The metabolite CVT-2738 (RS-94287) is the second most abundant metabolite. The mean AUC_{0-12} of CVT-2738 increased from 3,494 ng.h/mL in healthy subjects to 16,600 ng.h/mL in subjects with severe renal impairment (Crcl < 30 mL/min but not requiring dialysis). Other metabolites present in lower concentrations increased up to 9 fold.

Table 23: Study CVT 3016. Summary of mean steady state (Day 3) pharmacokinetic parameters of ranolazine metabolites following multiple oral doses of ranolazine PR (500 mg BD) to healthy and renally impaired subjects

Ranolazine/Metabolite	Parameter	Degree of Impairment			
		None (n = 8)	Mild (n = 7)	Moderate (n = 7)	Severe (n = 7)
Ranolazine	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	10,585 1,287 8.9	18,568 2,036 5.7	18,079 1,973 6.9	21,059 2,447 4.6
CVT-2512 (RS-88640)	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	1,432 132 20.4	1,095 105 23.7	1,749 158 63.3	3,158 318 94.3
CVT-2738 (RS-94287)	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	3,494 325 11.4	6,335 605 12.5	13,140 1,255 21.9	16,600 1,526 38.4
CVT-2514 (RS-88390)	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	4,285 455 11.6	2,944 321 11.2	3,810 368 13.9	6,531 716 18.9
RS-89289	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	331 35.2 12.9	699 74.0 12.8	1,261 128 12.3	2,863 276 13.0
CVT-4786	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	2,743 339 8.99	5,554 643 6.35	12,310 1,275 6.72	28,080 2,720 7.64
RS-88681	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	352 43.4 14.0	691 64.9 20.7	1,125 103 23.1	1,540 144 35.6
RS-89983	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	373 37.7 10.6	408 40.0 11.6	394 39.4 13.9	402 41.2 14.5
RS-89961	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	616 68.0 9.87	1,078 110 7.70	1,321 131 8.63	1,567 156 15.0
RS-88597	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	517 61.1 13.7	580 64.4 9.74	986 100 14.4	996 104 15.6
RS-101647	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	569 53.0 13.6	967 94.1 18.5	1,845 178 25.8	2,836 267 78.4
RS-88772 & RS-88835	AUC_{0-12} (ng•h/mL) C_{max} (ng/mL) $t_{½}$ (h)	372 39.9 16.2	830 83.3 12.3	1,049 103 14.0	1,356 133 17.3

There was little difference in the PK of ranolazine between the healthy and the subjects with mild hepatic impairment however there was a 1.69 and 1.35 fold increase in AUC and C_{max} of ranolazine, respectively between the mildly and moderately impaired groups. The pharmacokinetics of various metabolites were also altered in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B).

Population PK study CVT303.019-C, examined intra and inter individual variability in data from 12 PK/PD studies. Inter subject variability was high and estimated, respectively, at coefficient of variation (CV) = 23.1%, 106%, 97.1%, and 54.7% for the absorption rate constant (KA), Michaelis-Menten constant (KM), apparent volume of distribution (V/F) and apparent oral clearance (CL/F) parameters, respectively. The covariates of body weight, renal function, heart failure of the New York Heart Association (NYHA) Class III or IV, and presence of diltiazem were identified as factors affecting ranolazine PK. Specifically, low body weight, impaired renal function, heart failure of NYHA Class III or IV,

or the presence of diltiazem were estimated to reduce the clearance of ranolazine and increase the exposure of ranolazine. With the exception of very severe renal impairment (Crcl of 10 mL/min/1.73m^2), these factors are estimated to increase ranolazine plasma concentrations by less than 50%.

Extensive drug interaction studies were performed. The following medicines affected exposure to ranolazine:

- Potent CYP3A4 inhibition (ketoconazole); 3 to 4 fold increases in mean plasma concentrations of ranolazine.
- Moderate CYP3A4 inhibition (diltiazem); dose dependent increase in ranolazine plasma concentrations between 1.52- to 2.39 fold.
- Inhibition of CYP2D6 (paroxetine); mean 23% increase in ranolazine AUC.
- Verapamil increased ranolazine average plasma concentrations 2.25 fold. The sponsor has postulated that this effect is likely to be inhibition of P-gp in the gut, increasing the bioavailability of ranolazine.
- Potent CYP3A4 induction (rifampicin); AUC_{τ} reduced to about 5% of baseline.

Ranolazine affected the metabolism of the following medicines when co-administered:

- Metoprolol; mean 82% increase in $AUC_{0-\infty}$
- Dronedarone; mean 20% increase in the AUC_{τ} for ranolazine and a 30% increase in the AUC_{τ} for dronedarone in healthy subjects, less effect in subjects with AF.
- Metformin; mean 80% increase in AUC_{τ}
- Atorvastatin; mean 30% increase in AUC_{τ}
- Simvastatin; mean 50 - 100% increase in AUC_{τ}
- Digoxin; mean 60% increase in AUC_{0-24}
- Warfarin; increased prothrombin time. This was assessed with ranolazine IR in 4 healthy control subjects.

Pharmacodynamics

The anti-anginal effect of ranolazine is thought to be mediated by inhibition of the late sodium current in cardiac cells leading to a reduction of intracellular sodium accumulation and consequent reductions in intracellular calcium, possibly resulting in an improvement in myocardial relaxation and decreased left ventricular diastolic stiffness. Inhibition of the late sodium current by ranolazine is supported by the significant reduction in QTc interval and improvement in diastolic relaxation seen in a study of 5 patients with long QT syndrome.

In a study in patients with heart failure ranolazine was associated with statistically significant decreases in resting LVEDP (−2.13 ± 3.961 mm Hg; p = 0.042), resting pulmonary capillary wedge pressure (PCWP; −2.08 ± 3.166 mm Hg; p=0.044), and mean PAP under paced conditions (−1.76 ± 2.381 mm Hg; p = 0.016). There were no significant effects on other haemodynamic parameters including relaxation kinetics. Subjects received ranolazine via an IV bolus then infusion, followed by oral dosing. Cardiac effects were noted within 60 minutes of commencement of the bolus infusion.

The effect of ranolazine on cardiac function in patients with congestive heart failure was evaluated in studies RAN075 and CVT 3021. Even in patients with severe heart failure, stroke volume and ejection fraction remained unchanged with exposure to ranolazine, and

no significant increase in end-diastolic pressure was observed. There was no evidence that ranolazine produces a clinically significant negative inotropic effect.

The effect of ranolazine on rate pressure product (RPP) was examined in 3 studies. These studies indicate that statistically and clinically significant improvements in exercise performance can be achieved with ranolazine in the absence of effects on RPP. A reduction in RPP is seen at higher ranolazine doses but this reduction is smaller than that seen for calcium channel and beta-blockers.

The effects of ranolazine on cardiac ventricular repolarisation characterised by increased T wave amplitude and prolongation of the QTc interval are dose and plasma concentration dependent. Ranolazine prolonged QTc interval in a dose related manner at high plasma concentrations (4,000 to a target concentration of 15,000 ng/mL). The slope of the relationship between the plasma concentration of ranolazine and the change in QTc from baseline was approximately 2.29 msec per 1,000 ng/mL (range of individual slopes 0.87 to 4.61 msec) when using the individually optimised correction formulae. There was no gender difference in the slope. No subject had increased QTc from baseline by more than 60 msec in any of the recorded ECGs, based on the median QT interval for each ECG.

Comparable increases in QTc were observed in subjects with CHF (NYHA Class III/IV) and ranolazine concentrations of up to approximately 9,000 ng/mL. In subjects with mild or moderate hepatic impairment ranolazine was associated with mean QTcF values about 25 to 29 msec higher in the hepatic impairment groups than in controls. QTcF values exceeding 480 msec were observed in 2 subjects with moderate hepatic impairment. ranolazine ER at a dose of 500 mg BD had no effect on QTc in healthy or subjects with renal impairment.

An analysis of individually optimised corrected QT, prolongation of the optimally corrected QTc interval from baseline in the presence of ranolazine 1,000 mg BD and ketoconazole was found to be 23.09 msec (CI 16.25–29.94 msec). When corrected for the finding on placebo the increase in optimally corrected QTc interval versus the corresponding change on placebo was 19.77 msec (95% CI: 11.08–28.45 msec). None of the individual QTc prolongations following the highest dose of ranolazine (1,000 mg BD) exceeded 40 msec and the threshold of 30 msec was reached by four male subjects at the high dose of ranolazine. No pro-arrhythmic effects were observed in 3,162 patients treated with Ranexa based on 7 day Holter monitoring in the MERLIN-TIMI 36 study.

There were 4 dose finding studies, 3 using an IR formulation and one a PR formulation. IR doses to 400 mg TDS and PR doses to 1,500 mg BD were examined. Study CVT3013 was nominated as a pivotal study. This was a double blind, randomised, placebo controlled, 4 period crossover, multiple dose study of ranolazine PR as monotherapy for chronic stable angina pectoris at doses of 500 mg BD, 1,000 mg BD and 1,500 mg BD. It was conducted during 1997 to 1999. Patients received 1 week of treatment with each of the 4 treatment regimens in randomised order. Inclusion criteria for this study are presented below.

Summary inclusion criteria for Study 3031 (monotherapy with increasing doses of ranolazine PR).

Diagnosis and criteria for Inclusion to placebo qualifying phase, patients must have:

- Been at least 21 years old
- Had at least a 3 month history of chronic, stable angina pectoris that was triggered by physical effort and relieved by rest and/or sublingual nitroglycerin
- Had a history of documented coronary artery disease (CAD)
- Had improvement or control of angina or ECG signs of ischemia when treated with any combination of beta blockers, calcium entry blockers, or long-acting nitrates

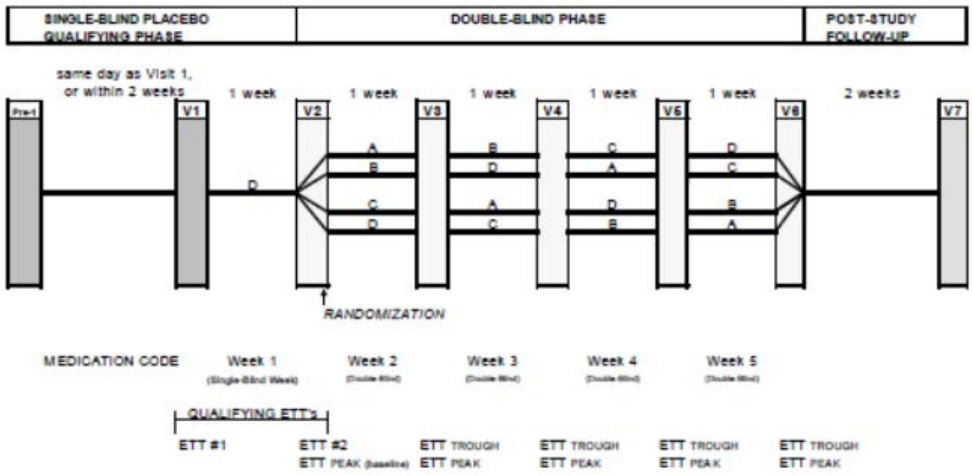
- Been willing to discontinue anti-anginal therapy 48 hours before Visit 1 and for the duration of the study
- Been willing to maintain stable tobacco usage habits throughout the study
- Female patients must have been post-menopausal, sterilised, or using approved contraceptive drugs or devices, and not breast feeding.

Patients must have successfully completed the placebo qualifying phase and met the following inclusion criteria based on results of the 2 ETTs conducted during that phase:

- Exercise duration was ≥ 3 and ≤ 9 minutes using a Modified Bruce protocol
- Exercise duration between the 2 qualifying ETTs did not differ by more than 20% of the longer of the 2 times and did not differ by more than 60 seconds
- Primary reason for stopping the 2 qualifying ETTs must have been angina
- Presence of definite ECG signs of myocardial ischemia during both qualifying ETTs (that is, 1 additional mm of horizontal or down sloping ST segment depression beyond baseline and at least 1 mm below the isoelectric line) must have been present in at least 1 standard ECG lead.

Efficacy was primarily assessed by Exercise Treadmill Tests (ETTs) at the end of each treatment week (Visits 3, 4, 5, and 6). At each weekly visit, ETTs were performed using a modified Bruce protocol on motor driven treadmills at time points coinciding with trough and peak plasma ranolazine concentrations. The study design is shown in Figure 3. The primary efficacy variable was symptom limited exercise duration using a Modified Bruce exercise protocol at the approximate time of trough ranolazine plasma concentration. Other efficacy variables assessed at trough were time to onset of angina, time to 1 mm ST segment depression, maximum ST segment depression, and primary reason for stopping exercise.

Figure 3: CVT3031 Study design



A = 500 mg Ranolazine SR BID
B = 1000 mg Ranolazine SR BID
C = 1500 mg Ranolazine SR BID
D = Placebo

Comparing ranolazine PR 500 mg BD, 1,000 mg BD and 1,500 mg BD with placebo, dose related increases in exercise duration at 12 hours post dose (trough plasma concentration) were seen with a mean increase in exercise duration of 45.9 sec (95% CI: 30.2, 61.7), 33.7 sec (95% CI: 18.1, 49.2) and 23.8 sec (95% CI: 8.2, 39.43) in the ranolazine PR 1,500 mg, 1,000 mg and 500 mg groups, respectively. The 1,500 mg BD dose was associated with increased adverse events (AEs) leading to discontinuation and the

dose range to 1,000 mg BD was selected for Phase III studies. Results are shown in Table 24.

Table 24: Study CVT3031. Mean difference compared to placebo in ETT duration at peak levels of ranolazine (sec) All/near-completers population and ITT population

Population	Statistic	Ran SR 1500 mg vs Placebo	Ran SR 1000 mg vs Placebo	Ran SR 500 mg vs Placebo
All/Near Completers [1]	Mean Difference	55.5	50.1	29.3
	S. E. of Mean Difference	7.3	7.2	7.2
	95% Confidence Interval	[41.2, 69.8]	[36.0, 64.2]	[15.2, 43.4]
	P-value	<0.001**	<0.001**	<0.001**
ITT [2]	Mean Difference	55.6	51.5	28.7
	S. E. of Mean Difference	7.8	7.3	7.2
	95% Confidence Interval	[40.4, 70.8]	[37.3, 65.8]	[14.6, 42.9]
	P-value	<0.001**	<0.001**	<0.001**

* 0.010 < p-value ≤ 0.050; ** p-value ≤ 0.010.
[1] A/NC Population analyzed using ANOVA for cross-over study design with effects for pooled site, patient within pooled site, period, and treatment
[2] ITT Population analyzed using GEE with effects for baseline ETT duration, pooled site, period, and treatment.
Note: Multiple comparisons adjusted for using closed testing and union intersection principles.
Note: Ran SR = Ranolazine SR
Data Source: Tables 2.1.2 and 2.2.2

Additional support for the proposed dose regimen was available from the ranolazine IR studies conducted from 1989 to 1993 (RAN072, RAN080 and RAN1514) and described in Attachment 2 demonstrated that mean trough ranolazine plasma concentrations of at least 800 ng/mL were required for efficacy (that is prolonged exercise times); the PR tablet at doses ≥ 750 mg BD maintained these plasma concentrations at peak and trough (4 and 12 hours post-dosing, respectively), while 500 mg BD provided this plasma concentration only at peak (RAN0114, a PK study).

Efficacy

While 4 studies were nominated as pivotal studies the study with the most pertinent information is Study CVT 3033 (CARISA) described in Attachment 2. This was a double-blind, randomised, placebo controlled study of add-on ranolazine PR (750 or 1,000 mg BD) in 823 subjects with chronic stable angina pectoris treated with a single anti-anginal agent (diltiazem CD 180 mg daily, atenolol 50 mg daily or amlodipine 5 mg daily). This study had 3 phases: a qualifying phase during which 2 ETTs were performed, a 12 week treatment phase with trough ETTs performed at Weeks 2, 6, and 12 and a 2 day rebound assessment phase during which patients received either the same treatment they had been given during the 12 week double blind phase or placebo.

To qualify for the double blind portion of this study, exercise duration was to be symptom-limited to 3 to 9 minutes with angina cited as the primary reason for stopping exercise, and there were to be definite signs of myocardial ischemia on ECG (that is showing at least a 1 mm ST segment depression) during ETT. The primary efficacy variable was change from baseline in ETT duration at trough at Week 12 using the last observation carried forward (LOCF). The multiple comparison issue was addressed by a two stage, step down procedure. This was based on the closed testing and union intersection principles. No adjustments were made for any of the secondary or supportive analyses. The Modified Bruce Protocol was used to conduct the ETT.

Secondary efficacy variables included: change from baseline in exercise duration at peak; change from baseline in time to angina onset, time to 1 mm ST segment depression, maximum ST segment depression and reasons for stopping ETT at trough and at peak; angina frequency during 12 weeks; change from baseline in ETT duration at trough on

ranolazine discontinuation. Time to angina, time to 1 mm ST-segment depression, angina frequency and nitroglycerin use all reduced with use of ranolazine as described in Attachment 2.

There were 823 randomised subjects with 43% on atenolol, 31% on amlodipine and 26% on diltiazem. The disposition of subjects is shown in Figure 5 of Attachment 2 and results for mean change from baseline in ETT duration at trough levels of ranolazine at Week 12 Intent-to-treat (ITT) population are shown in Tables 12 and 14 of Attachment 2. ETT at baseline was between 414 and 418 seconds across the treatment groups. The mean changes from baseline at the Week-12 assessment (LOCF) were 91.7s (placebo), 115.4s (ranolazine 750 mg) and 115.8 s (ranolazine 1000 mg). The differences from placebo for the Week-12 (LOCF) time point were 23.7 seconds for ranolazine 750 mg ($p = 0.03$) and 24.0 s for ranolazine 1000 mg ($p = 0.29$). Of particular note effects on angina frequency and exercise tolerance were considerably smaller in women than in men. While the Delegate could not locate an analysis of ETT by sex in the study report the US PI description of this study states that the improvement in ETT in females was about 33% of that in males at the 1000 mg BD dose level. The sponsor is requested to confirm this in the Pre-ACPM response.

The remaining studies nominated as pivotal do not provide pivotal evidence of the safety and efficacy of ranolazine PR as an add-on treatment in the management of stable angina. Study 3037 assessed concomitant treatment of ranolazine 1000 mg BD with amlodipine 10 mg daily only and the double blind assessment period was only 6 weeks. Efficacy was measured through evaluation of the frequency of angina attacks and nitroglycerin use. While combination amlodipine and ranolazine did result in a statistically significant reduction in the angina episode rate and nitroglycerine use these are not recommended primary endpoints for pivotal studies of treatments for stable angina and the proposed dose regimen of ranolazine was not used.

Study 3036 (MERLIN-TIMI) was conducted to determine whether ranolazine was superior to placebo in reducing the rate of cardiovascular (CV) death, myocardial infarction (MI), or recurrent ischemia during long term treatment of patients with non-ST elevation acute coronary syndrome (ACS) receiving standard therapy. The effect on ranolazine on duration of ETT at Month 8 of treatment was the 6th secondary efficacy endpoint. That study did allow ranolazine doses of 375 mg BD and 500 mg BD, though subjects were not required to have stable angina. Results of the ETT assessment are shown in Table 21 in Attachment 2 and suggest an advantage from use of ranolazine however all doses are grouped together and compared with placebo and there is no baseline ETT on which to assess differences between the placebo and ranolazine treated groups. Furthermore given the multiplicity of secondary endpoints the statistical assessment of that result does not have a firm basis. Both Studies CVT 3036 and CVT 3037 suggest that ranolazine may be more effective in increasing ETT in males compared to females however there is no firm statistical basis to support that claim due to the limitations of study design to determine that difference.

Safety

As of July 2012, the ranolazine clinical program has included 11,210 subjects (healthy, chronic angina, non-ST elevation ACS or type 2 diabetes mellitus) with 7,451 who had received ranolazine IV, IR or PR formulations. The population of most relevance for the proposed indication was a subset of the integrated safety database comprising the Phase II and III controlled angina studies with the PR formulation (Studies CVT 3033, CVT 3037, CVT 3031 and RAN2240). This included 1,030 patients treated with ranolazine PR and 738 with placebo. The mean exposure duration in that subset was 61 days for ranolazine and 52 days for placebo. Study CVT 3036 included 3,268 subjects given ranolazine and 3,273 given placebo with 54% of subjects having a history of angina. In that study the mean

exposure (IV and oral dosing) was 279 and 297 days in the ranolazine and placebo groups, respectively.

The most common AEs associated with ranolazine are nausea, constipation and dizziness. There is a marked, dose related increase in nausea when the dose was increased above 1,000 mg BD. Table 30 in Attachment 2 shows selected dose related AEs by target ranolazine concentration from the ranolazine IV Study, CVT 3111. Nausea, dizziness, headache, blurred vision, diplopia, somnolence, vasovagal syncope and lethargy were strongly positively correlated with serum ranolazine concentration. There was no indication of increased unstable angina, myocardial infarction, cardiac failure or atrial fibrillation in the long term study (Study CVT 3036), as shown in Table 32 in Attachment 2. The most frequent AE leading to study discontinuation in Study 3036 was nausea (5% ranolazine versus 2% placebo). There was no evidence that ranolazine increased HbA1c in the overall population or in patients with diabetes at enrolment (Table 33 in Attachment 2 refers).

There was no indication of altered mortality or of Clinical Events Committee (CEC) adjudicated cardiovascular deaths. A small (0.1 mg/dL) increase in mean serum creatinine in the Phase II/III studies was attributed by the sponsor to inhibition of tubular secretion of creatinine by ranolazine. Small changes in haematology parameters were seen including a mean reduction in haemoglobin (-0.5 g/dL) in the Phase II/III studies. While there was no mean reduction in Hb in the longer term Phase III study (CVT 3036), of subjects with normal haemoglobin at baseline, 19% of ranolazine and 14% of placebo subjects had shifted below normal at the final visit. Dose-related changes to ECG parameters are shown in Table 34 of Attachment 2. These included small (2 to 5.4 msec) increases in QTc which were dose related. In Study CVT3031, there was a reduction in T wave amplitude and increased frequency of notched T waves with increasing ranolazine dose. At peak the proportion of subjects with notched T waves was 2%, 1%, 3% and 6% in the placebo and ranolazine 500 mg, 1000 mg and 1500 mg bid groups, respectively.

Ranolazine did not significantly affect heart rate or blood pressure at doses to 1000 mg BD. Increasing age, gender and presence of diabetes did not affect the safety endpoints.

Ranolazine has extensive post-market safety data and 15 cumulative post-market safety reviews have been conducted as described in Section 8 of Attachment 2. Major changes to the CCDS have included a dose reduction for simvastatin to a maximum to 20 mg daily when co-administered with ranolazine and the addition of text regarding the potential need for dose adjustment of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range when co-administered with ranolazine. Examples of relevant sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range to be included in the CCDS are simvastatin, lovastatin, cyclosporine, tacrolimus, and sirolimus.

Risk management plan

RMP evaluation

There were no RMP reviewer objections to approval. The advice of ACSOM was not sought. A Patient Alert Card (PAC) is provided to patients in the EU. The card informs patients about the main interactions, contraindications and precautions of ranolazine. It has not been proposed for Australia. The sponsor has advised that in Australia, the information presented in the EU PAC will be prominently included in the Australian Consumer Medicine Information (CMI). This is acceptable from a RMP perspective.

The RMP reviewer recommended that the following be included as a condition of registration for Ranexa:

Implement EU-RMP Version 7.2 (dated 6 March 2013, DLP 26 July 2011) with Australian Specific Annex Version 1.1 (dated 8 May 2015) and any future updates as a condition of registration.

Delegate's considerations

Discussion

Preclinical studies suggest the mechanism of action of ranolazine differs from those induced by beta-blockers, calcium channel antagonists, nitrates, K channel openers, and sinus node inhibitors which reduce myocardial oxygen demand via direct myocardial effects, indirectly by complex effects on haemodynamic determinants and in the case of calcium channel antagonists, nitrates, and K channel openers possibly by improving blood flow and thus oxygen supply to the heart.

Ranolazine has complex pharmacokinetics, potential for multiple drug interactions and has been proposed for use in a population that is more likely to be taking multiple potentially interacting medications and to have reduced renal function relative to the general population due to greater age and/ or cardiovascular disease. Absorption is highly variable and serum levels are significantly affected by both hepatic and renal impairment. An extensive list of contraindications has been proposed including moderate to severe hepatic impairment and severe renal impairment (CKD Stages 4 and 5). In the USA Child-Pugh Class A hepatic impairment is also a contraindication. The basis for this appears to be a 3 fold increase in QT prolongation seen in cirrhotic patients with mild to moderate hepatic impairment given ranolazine.

To address use in patients with renal impairment the sponsor was requested to provide commentary of dose adjustment. The sponsor has proposed instead to describe the extent of change in AUC of ranolazine in subjects with mild, moderate, and severe renal impairment.

No dose adjustment has been proposed. The Delegate noted that in the US PI no dose adjustment is recommended for individuals with renal impairment and that it is recommended that renal function be periodically monitored in patients with moderate to severe renal impairment and ranolazine discontinued if acute renal failure develops. Changes in the AUC of ranolazine in subjects with mild to moderate hepatic impairment were small and dose adjustment would not need to be considered. Dose adjustment has been recommended for strong CYP3A4 inhibitors.

Section 6.2 of the Guideline[26] recommends the following with regard to dose-response studies:

- Dose-response studies should be randomised, placebo-controlled and double-blinded using at least three dosages to establish the clinically useful dose range as well as the optimal dose.
- These studies should preferably be designed as parallel group studies and should last at least six weeks.
- The results of the dose-response studies of a new antianginal drug should provide robust evidence of its efficacy as compared to placebo, including precise quantitative estimates of its beneficial effects.

Dose-response was explored in Study CVT 3031. This was a crossover rather than parallel group study, treatment duration at each dose was 1 week rather than 6 weeks, the run-in period was shorter than recommended, and subjects could have been included too soon after revascularisation (only 2 months instead of the recommended 6 months). In

addition, there were no washouts between periods and, whilst there was no statistically significant interaction on assessment of carryover, the data from the first period found no improvement in exercise duration at trough.

In that study the mean ETT did increase with increasing dose between 500 mg BD and 1000 mg BD but there was no statistical comparison between the various doses. Dose response was not firmly established. Each dose was superior to placebo for increase in ETT. The primary efficacy measure was assessed after subjects had been taking each dose for one week rather than 6 weeks as is recommended in the Guideline. The committee is requested to comment on whether is considered adequate to support monotherapy use when other anti-angina treatments are not tolerated. If this is agreed then the committee is requested to specify how many treatments are required to be not tolerated prior to use of ranolazine as monotherapy.

Study CVT 3033 is the pivotal efficacy study and was conducted over 15 years ago prior to the current (2006) version of the Guideline.[26] Additional studies of the IR and IV formulations were conducted from the 1980 to 2000s. Those studies have limited efficacy information relevant to the proposed indication.

Study CVT 3033 was conducted over a sufficient period of time, had appropriate design, subject selection and efficacy criteria. In this study ranolazine PR was given as add-on therapy to one of 3 different anti-angina treatments. The study was not designed to determine the extent of increase in ETT for each baseline treatment and each dose. So it is not possible to examine whether the extent of improvement in ETT varies with the baseline anti-angina treatment. The doses of ranolazine used in that study were not fully consistent with the dose range proposed. Doses of 500 mg BD and 750 mg BD have been proposed yet the pivotal study assessed doses of 750 mg BD and 1,000 mg BD. No additional improvement in ETT was seen with an increase in dose between 750 mg BD and 1,000 mg BD in that study.

Evidence for efficacy of the proposed 500 mg BD dose is based primarily on Study CVT 3031 in which showed a trend towards increased response with increased dose when ranolazine PR was given as monotherapy, though statistical comparisons between doses were not performed. CVT00204, a PK/PD analysis described in Attachment 2 also suggested a dose response though using mostly the IR dose form.

Add-on therapy with other anti-angina medicines hasn't been explored. It is not clear whether ranolazine should be restricted to add-on therapy only to the anti-angina medicines in the pivotal study or whether ranolazine could be considered as add-on therapy for other anti-angina medicines in the same drug classes or other classes.

The extent of improvement in ETT compared with placebo is similar to that seen with ivabradine when given concomitantly with atenolol. The absolute difference from placebo at Week 12 trough was 23.7 seconds for ranolazine 750 mg BD ($p = 0.03$) and 24.0 s for ranolazine 1,000 mg BD ($p = 0.29$). From a baseline of mean ETT of 414 s to 418 s, the difference represents approximately 5.6% improvement in ETT compared with placebo. ETT is inherently variable. Of note an improvement in ETT in the region of 22% was seen over the time between baseline and Week 12 in the placebo group. This shows the importance of including a placebo arm in studies of this type.

The adverse effects attributable to ranolazine appear to be manageable in the context of the proposed indication. The major concern relates to the variable pharmacokinetics and high risk of drug interactions. The proposal to commence with the 375 mg BD dose is accepted in this context, though there is minimal evidence that this dose has clinically significant efficacy. Prescribers and patients should be aware of potential dose related adverse effects so that the dose is not escalated should symptoms of too high a dose occur (for example nausea, dizziness).

Summary of Issues

Ranolazine has variable absorption, potential for multiple drug interactions and serum levels are significantly affected by both hepatic and renal impairment. Dose adjustment may be required.

The dose-finding study was conducted around 15 years ago and was not designed consistent with current recommendations.

There is only one adequately designed pivotal study to demonstrate efficacy for the proposed indication and that is as add-on therapy.

The indication is ambiguous. The proposed indication is for add-on use however this is followed with a statement that implies monotherapy use under certain circumstances. A clear indications statement is required to avoid confusion.

Efficacy may be less in females compared to males. The sponsor has been requested to clarify this point.

Proposed action

The Delegate had no reason to say, at this time, that the application for Ranexa should not be approved for registration, subject to further negotiation of the PI.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Should monotherapy be considered within the indication? The committee is requested to comment on whether the monotherapy dose-finding Study CVT 3031 provides adequate evidence to support monotherapy use when other anti-angina treatments are not tolerated. If this is agreed then the committee is requested to provide advice on the number of treatments not be tolerated prior to use of ranolazine as monotherapy. An amended indication may follow from this advice.
2. Should concomitant anti-angina treatment be specified in the indication or products assessed for concomitant use be identified only in the CLINICAL TRIALS section of the PI?
3. Should ranolazine be given with multiple concomitant anti-angina therapies or only one other therapy as in the pivotal clinical trial?
4. Should there be specific advice on dose reduction for individuals with moderate or severe renal impairment?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Overall recommendation

The sponsor agrees with the Delegate on the recommendation for the approval of Ranexa 375 mg, 500 mg and 750 mg for the treatment of angina as add-on therapy. In this regard the sponsor deems that the proposed wording for the indication is not ambiguous as it clearly indicates that the product has to be used as add-on therapy, describing then the two scenarios: not stabilised patients or intolerant patients.

The sponsor would also like to confirm that the issue regarding the efficacy in females has already been addressed with the submission of a revised version of the PI provided on

25 February 2016 in response to the review of the second round clinical evaluation. This revision involved inserting a gender section similar to the US-PI.

With reference to the hepatic and renal impairment patients, the sponsor deems that no further changes are necessary in the PI since the product is contraindicated in moderate to severe hepatic impairment patients and in severe renal impairment patients, while a careful titration is recommended in mild hepatic impairment and in mild to moderate renal impairment patients.

The sponsor does not agree with the substitution in the PI Adverse Effects section of the System Organ Class table with Table 13 from module 2.7.4 of the dossier. The sponsor believes a lot of adverse reactions would be lost and therefore not available for prescribing physicians.

Finally the sponsor deems that since the Adverse Events data reported in the PI are the results of the pooling of all the Clinical Trials submitted, the description of these should be maintained in the clinical trials section.

Summary of the issues raised

1. Ranolazine has variable absorption, potential for multiple drug interactions and serum levels are significantly affected by both hepatic and renal impairment. Dose adjustment may be required.
2. The dose-finding study was conducted around 15 years ago and was not designed consistent with current recommendations.
3. There is only one adequately designed pivotal study to demonstrate efficacy for the proposed indication and that is as add-on therapy.
4. The indication is ambiguous. The proposed indication is for add-on use however this is followed with a statement that implies monotherapy use under certain circumstances. A clear indications statement is required to avoid confusion.
5. Efficacy may be less in females compared to males. The sponsor has been requested to clarify this point.

Sponsor comments

Ranolazine has variable absorption, potential for multiple drug interactions and serum levels are significantly affected by both hepatic and renal impairment. Dose adjustment may be required.

Sponsor comments:

As discussed in the Overall Recommendations section the sponsor would like to highlight that in the proposed PI, ranolazine is contraindicated in both severe renal impaired patients and in moderate to severe hepatic impaired patients. According to the dose-diagram included in the Dosage and Administration section it states: 'ranolazine should be administrated with caution in mild to moderate renally impaired patients and in mildly impaired hepatic patients'. The sponsor believes that this provides adequate information for prescribing physicians in the treatment of this patient group and that no additional amendments should be introduced in the PI.

The indication is ambiguous. The proposed indication is for add-on use however this is followed with a statement that implies monotherapy use under certain circumstances. A clear indications statement is required to avoid confusion.

Sponsor comments:

As explained in the Overall Recommendations section, the sponsor deems that the proposed wording is not ambiguous and that for this no changes should be introduced.

Efficacy may be less in females compared to males. The sponsor has been requested to clarify this point

Sponsor comments:

As explained in the Overall Recommendations section, the sponsor has submitted a revised version of the PI on 25 February in response to the Clinical Evaluator's Comments. In line with the US-PI, the following Gender section was included:

"Gender Effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In CARISA, the improvement in Exercise Tolerance Test (ETT) in females was about 33% of that in males at the 1000 mg twice-daily dose level."

Advice sought

1. *Should monotherapy be considered within the indication? The committee is requested to comment on whether the monotherapy dose-finding study CVT3031 provides adequate evidence to support monotherapy use when other anti-angina treatments are not tolerated. If this is agreed then the committee is requested to provide advice on the number of treatments not be tolerated prior to use of ranolazine as monotherapy. An amended indication may follow from this advice.*

Sponsor comment:

The sponsor confirms that the wording of proposed indications reflects the use of Ranexa only in patients who have initially been shown to be inadequately controlled by or intolerant to other anti-anginal drugs. The proposed indication is based on the results of CARISA (CVT 3033), ERICA (CVT 3037), and MERLIN TIMI (CVT 3036).

2. *Should concomitant anti-angina treatment be specified in the indication or products assessed for concomitant use be identified only in the CLINICAL TRIALS section of the PI?*

Sponsor comment:

The sponsor deems that the concomitant anti-angina treatments should be specified only in the PI CLINICAL TRIAL section, as already accepted by the EMA and FDA.

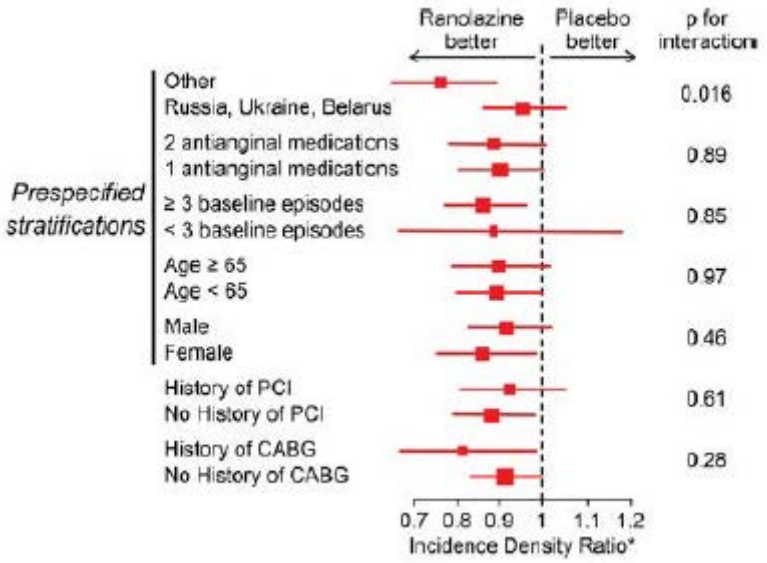
3. *Should ranolazine be given with multiple concomitant anti-angina therapies or only one other therapy as in the pivotal clinical trial?*

Sponsor comment:

The sponsor acknowledges the comment and would like to provide the following considerations to support the use of ranolazine with multiple concomitant anti-angina therapies.

In the submitted clinical trial GS-US-259-0107 (TERISA), patients were stratified according to whether they were taking 1 or 2 anti-anginal medications on top of ranolazine reporting no significant difference between the 2 groups in terms of average weekly number of anginal episodes over the last 6 weeks of therapy. (1 versus 2; p interaction = 0.89), See Figure 4.

Figure 4: Study GS-US-259-0107 response rates for the placebo and ranolazine groups for anginal episodes



In the above study, 420 patients have been identified on two anti-anginals at baseline, of whom, 210 were randomised to placebo and 210 to ranolazine. At 42 days there was a trend to improvement with ranolazine versus placebo, even if not statistically significant (p = 0.075), most probably due to the insufficient number of patients (see Table 25).

Table 25: Weekly angina frequency - generalised linear model (Last 42 days of (on-treatment data) by number of anti-anginal medications - Full Analysis Set

		Placebo (N=465)	Ranolazine (N=462)	p-value
Number of Concomitant Anti-anginal Medications: ≥ 2				
Baseline				0.85
	N	206	203	
	Mean (SD)	6.7 (4.24)	6.7 (4.22)	
	Median	5.3	5.7	
	Q1, Q3	3.7, 8.7	3.7, 8.5	
	Min, Max	1.0, 24.5	1.0, 26.3	
	LS Mean [95% CI]	6.5 [6.03, 7.10]	6.5 [5.96, 7.04]	
	Incidence Density Ration (95% CI)		0.99 [0.88, 1.11]	
Last 42 Days				0.075
	N	206	203	
	Mean (SD)	4.9 (4.64)	4.5 (4.84)	
	Median	3.1	3.2	
	Q1, Q3	1.8, 6.5	2.0, 5.3	
	Min, Max	0.0, 25.2	0.0, 39.4	
	LS Mean (95% CI)	4.1 [3.76, 4.51]	3.7 [3.34, 4.03]	
	Incidence Density Ration (95% CI)		0.89 [0.79, 1.01]	

Additionally, the sponsor would like to highlight that the information coming from the MERLIN TIMI 36 study (CVT 3036), which included 3,565 (54%) patients with a history of chronic angina (1,776 placebo and 1,789 ranolazine). Approximately 70% of these patients were treated with anti-anginal drugs belonging to two or more classes (88% with beta-blockers, 71% with nitrates/coronary vasodilators, and 40% with calcium channel blockers).

The study confirmed the anti-anginal effect as supported by a 23% risk reduction (p = 0.019) of worsening angina that required additional therapy. In addition, the need for additional anti-anginal medications was lessened in the ranolazine group compared to the placebo group, both in terms of number of anti-anginal medications prescribed, (p = 0.002 at Final Visit) as well as the time to initiation of additional anti-anginal therapy with a relative risk of 0.76 (95% CI 0.64 to 0.90; p = 0.002). Finally, fewer ranolazine patients required an anti-anginal medication dose increase (p = 0.025).

In conclusion, the sponsor considers that the above data, in addition to those collected in the pivotal study, support the use of ranolazine as add-on therapy for symptomatic treatment of angina.

4. *Should there be specific advice on dose reduction for individuals with moderate or severe renal impairment?*

Sponsor comment

Please refer to the comments in point 1 included in the Summary Issues section and also in the Overall Recommendations section.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Ranexa prolonged release tablet containing 375 mg, 500 mg and 750 mg of ranolazine for the indication;

> *Ranexa 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 anti-anginal therapies (such as beta-blockers and/or calcium antagonists).*

In making this recommendation the ACPM;

- noted that despite this product being developed more than 30 years ago the mechanism of action is unknown.
- noted that the studies submitted did not entirely fulfil current Guidelines, which suggest particularly that background anti-anginal therapy should be maximised and standard efficacy outcomes should be used.
- noted that the one adequately designed pivotal study submitted to support efficacy for the proposed indication was as add-on therapy.
  - the trial population was very symptomatic and undertreated in CARISA, so not representative of an expected population.
- was of the view that analysis on the pivotal trial "efficacy evaluable" patients, did not show positive efficacy (for the doses being considered) because in the patients who fulfilled the inclusion criteria the effect of treatment with 750 mg BD was not statistically significant. The committee noted that the ITT population analysis showed a statistically significant difference from the addition of 750 mg BD ranolazine.
- expressed concern that the level of efficacy demonstrated in females was not statistically significant thus reducing the potential treatment population.
- noted that no comment was made by the sponsor on two questions posed by the TGA.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Should monotherapy be considered within the indication? The committee is requested to comment on whether the monotherapy dose-finding study CVT 3031 provides adequate evidence to support monotherapy use when other anti-angina treatments are not tolerated. If this is agreed then the committee is requested to provide advice on the number of treatments not be tolerated prior to use of ranolazine as monotherapy. An amended indication may follow from this advice.*

The ACPM advised there was insufficient data to recommend monotherapy as Study CVT 3036 (MERLIN-TIMI) was not designed to determine efficacy of monotherapy and extrapolation / post hoc analysis of the pooled ETT data is tenuous at best.

2. *Should concomitant anti-angina treatment be specified in the indication or products assessed for concomitant use be identified only in the CLINICAL TRIALS section of the PI?*

The ACPM advised that the effect size of this medication is modest and given the high risk of adverse events from drug interactions evidence provided for use of Ranexa in treatment of stable angina pectoris is inadequate.

3. *Should ranolazine be given with multiple concomitant anti-angina therapies or only one other therapy as in the pivotal clinical trial?*

The ACPM advised there was insufficient evidence submitted to allow an informed answer to this question.

4. *Should there be specific advice on dose reduction for individuals with moderate or severe renal impairment?*

The complexity of the pharmacokinetics of ranolazine, the lack of understanding of the mechanism of action, multiple metabolites that have not been fully characterised, the variability of both T_{max} and the elimination half-life and the extensive but not fully explored interactions with other medicines (contraindications for concomitant administration of potent CYP3A4 inhibitors; of CYP3A4 inducers; of Class Ia or Class III antiarrhythmics) are such that providing suitable advice is problematic.

The PI statement "Careful dose titration is necessary in mild to moderate renal impairment" is considered less than adequate. Clearly close monitoring with many co-medications would be necessary and may explain some of the trial dropout rate.

The committee concluded that there was sufficient uncertainty regarding the drug's efficacy, mode of action, apparent decreased effectiveness in women and the possible metabolic and pharmacokinetic actions of drug metabolites that a negative benefit-risk appraisal was concluded.

Post ACPM negotiations

The Delegate in negotiation with the sponsor following the recommendation of the ACPM noted the following:

> The committee concluded that there was sufficient uncertainty regarding the drug's efficacy, mode of action, apparent decreased effectiveness in women and the possible metabolic and pharmacokinetic actions of drug metabolites that a negative benefit-risk appraisal was concluded. Although the ACPM had a negative recommendation the Delegate sees that there may be a role for ranolazine as a second line treatment in patients with stable angina who, while taking maximum tolerated doses of a beta-blocker or calcium channel blocker, continue to have disabling angina symptoms. It is in this context that the Delegate intends to

approve registration, subject to negotiation of the indication and PI for Ranexa (ranolazine).

The Delegate recommended the following amended indication

> *Ranexa is indicated in adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control.*

The sponsor agreed to the requested changes to the indication, the PI and the CMI.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ranexa ranolazine 375 mg, 500 mg and 750 mg modified release tablet blister pack, indicated for:

> *Ranexa is indicated in adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control.*

Specific conditions of registration applying to these goods

The ranolazine European Risk Management Plan (EU-RMP), version 7.2,6 March 2013, data lock point 26 July 2011), with Australian Specific Annex (version 1.1,8 May 2015, to be revised to the satisfaction of the TGA), included with submission PM-2015-00423-I-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Ranexa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi> .

Attachment 2. Extract from the Clinical Evaluation Report

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