European Medicines Agency
*Evaluation of Medicines for Human Use*

Doc.Ref.: EMEA/CHMP/30876/2008

**CHMP ASSESSMENT REPORT**

**FOR**

**LATIXA**

International Nonproprietary Name: ranolazine

**Procedure No. EMEA/H/C/805**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant CV Therapeutics Europe Limited submitted on 27 November 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Latixa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 1 June 2006.

The legal basis for this application refers to article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

**Scientific Advice**
The applicant did not seek scientific advice at the CHMP.

**Licensing status:**
Latixa has been given a Marketing Authorisation in USA on 27 January 2006.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Bengt Ljungberg** Co-Rapporteur: **Gonzalo Calvo Rojas**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 November 2006.
- The procedure started on 27 December 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2007 (The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 23-26 April 2007 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 April 2007.
- During the meeting on 18-21 June 2007 the CHMP agreed to the request from the applicant for a 3-month extension of clock stop to respond to the List of Questions.
- During the meeting on 17-20 September 2007 the CHMP agreed to an additional month extension of clock stop to respond to the List of Questions.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 1 November 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 January 2008.
- During the CHMP meeting on 21-24 January 2008 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- A clarification meeting via teleconference on the list of outstanding issues was held on 1 February 2008.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues on 15 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 March 2008

The applicant submitted further responses in preparation of the oral explanation on 13 March 2008.

- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's further responses to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Latixa on 24 April 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 April 2008.

# 2 SCIENTIFIC DISCUSSION

## 2.1 Introduction

Ischemic heart disease (IHD) is the most common, chronic, life-threatening illness in the western world, causing more deaths and disability and incurring grater economic costs than any other illness.

The primary consideration in the choice of pharmacological agents for treatment angina should be to improve prognosis. Aspirin and lipid-lowering therapy have been shown to reduce the risk of death and non-fatal myocardial infarction (MI) in both primary and secondary prevention trials. Beta-blockers also reduce cardiac events when used as secondary prevention in post-infarction patients and reduce mortality and morbidity among patients with hypertension. Diltiazem and verapamil are also useful in such circumstances although they should be avoided in the presence of significant left ventricular dysfunction. Nitrates are of value where there is left ventricular dysfunction. β-blockers are indicated in cardiac failure and some vascular selective long-acting dihydropiridines can be given cautiously in such patients. Patients with asthma and peripheral vascular disease may be best treated with a long acting nitrate or a calcium antagonist, although selective β-blockers may be given with caution.

Despite the increasing success of conventional medical therapeutic approaches and the continued development and improvement of mechanical revascularization approaches, a significant number of patients with IHD and angina pectoris cannot be successfully managed with currently available options. In addition, a substantial proportion of patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) do not achieve complete revascularization, and many of these patients continue to experience residual anginal symptoms of myocardial ischemia despite maximal medical therapy.

CVT Therapeutics Europe Limited has provided a complete/stand-alone application of a new active substance (Ranolazine) through a centralised procedure. This application is submitted in accordance with the article 8(3) in directive 2001/83/EC.

A previous procedure for ranolazine in the treatment of chronic angina pectoris was submitted in 2004 (Trebinex, prolonged release tablets 375 and 500 mg). This procedure, EMEA H/C/592, was withdrawn at Day 180 due to major deficiencies which precluded the authorisation of the product. Major safety concerns related to genotoxicity as well as safety concerns related to the risks for increased exposure due to drug interactions, were identified as the preclinical main issues, and efficacy on top of at least other conventional anti-anginal product, the clinical relevance of the effect and the clinical safety of the higher dose, were identified as the main clinical deficiencies.

The proposed indication reads as follows:

Latixa is indicated 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 betablockers and/or calcium antagonists). Due to its pharmacodynamic profile, Latixa may be particularly relevant for those patients in whom a decrease in heart rate or blood pressure, or increase in PR interval is undesirable.

The approved indication is:

Latixa is 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).

## 2.2 Quality aspects

### Introduction

Composition
Latixa contains ranolazine as the active substance. It is presented as film-coated prolonged-release tablets in three dosage strengths of 375 mg, 500 mg and 750 mg.
Each tablet core contains methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, hypromellose, sodium hydroxide and magnesium stearate.
The tablets are coated with an aesthetic film-coating having a different colour for each strength in order to facilitate identification of the different strengths by patients and to eliminate medication errors. The components of the light blue and orange film-coatings include the colorant, hypromellose, titanium dioxide, polyethylene glycol and polysorbate 80. The blue film-coating consists of the colorant, hypromellose, titanium dioxide, glycerol triacetate and lactose monohydrate.
The tablets are packaged either in blisters or high-density polyethylene (HDPE) bottles.

### Active Substance

The chemical name of ranolazine is (±)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl] piperazineacetamide.

Ranolazine is a white to off-white solid, very slightly soluble in water. It is freely soluble in aqueous buffered solutions at pH levels below 4.4 and soluble in several organic solvents e.g. dichloromethane and methanol. The chemical structure is well characterised by means of elemental analysis, UV, IR, $^{1}$H-NMR, $^{13}$C-NMR chemical ionization, electron impact mass spectra and x-ray diffraction.
Ranolazine exhibits a chiral center and is obtained as a racemic mixture that consists of a 1:1 ratio of (R) and (S) enantiomers. This is confirmed by demonstrating that ranolazine does not exhibit any optical rotation of plane polarized light in polarimeter measurements. Both enantiomers exhibit pharmacological activity.
Regarding polymorphism, crystallisation studies were conducted using different solvents, crystallization conditions and vapor diffusion experiments. In these studies three crystalline forms named as Form I, Form II, Form III and one amorphous form were identified. Form I is the only one that was thermodynamically stable, Form II and Form III are kinetically unstable. The synthetic process used for the synthesis of ranolazine has been shown to produce only Form I. Extreme conditions that are not relevant to the synthetic process are required to convert ranolazine to other solid-state forms (amorphous and two other crystalline forms, Form II and Form III).

- Manufacture

Ranolazine is manufactured using a three step synthetic process followed by purification, drying and milling. The starting materials are 2,6-dimethylaniline (2,6-DMA), chloroacetyl chloride (CAC), piperazine dihydrochloride and guaiacol glicydil ether (GGE). The synthetic process has been adequately described the critical process parameters have been identified and are controlled with appropriate in-process controls.
Data from four validation batches have been provided that demonstrate that the manufacturing process is capable to consistently produce batches of active substance that comply with the predefined specifications.
A detailed discussion about potential impurities and their origin has been provided in line with ICH Guideline Q3A(R). Three specified impurities arising from the route of synthesis and one arising from the staring materials have been identified. There are also eight unspecified potential impurities.

- Specification

The specifications were set according to ICH Q3A(R), Q3C and Q6A Guidelines taking into account analytical results from stability, clinical trials and toxicological studies.

The parameters included in the specifications are appearance, identification (IR, Optical rotation), assay (HPLC), organic impurities (HPLC), heavy metals (Ph.Eur.), residue on ignition (Ph.Eur), residual solvents (GC), melting range, water content, particle size distribution (laser diffraction), completeness of solution (USP).
In general terms, the proposed specifications are suitable to control the quality of the active substance and the analytical methods used are either compendial or have been satisfactorily validated.
The levels of the impurities are supported by the results of 10 commercial scale batches. Toxicological studies have been carried out for those organic impurities that exceed the limit of max.0.15% in order to qualify the levels proposed in the specification. Taking into account that there are not specific sources for inorganic impurities, only general methods of heavy metals and residue on ignition have been included in the specifications.

- Stability

Stability studies were carried out according to the ICH requirements. Accelerated stability studies have been performed in 40$^{o}$C/75 % RH with 3 primary batches of the active substance for 6 months. Long term and stability studies have been performed in 25$^{o}$C/60 % RH with 3 primary batches and 3 commercial batches for up to 48 months. Additionally, results from three annual stability batches have been provided. The packaging materials used in the stability studies simulate the commercial packaging.
The parameters tested included physical appearance, assay, impurities (specified, individual unspecified and total impurities) water content and particle size. The analytical methods used were the same as those used for routine controls and are stability indicating.
The results have shown that there are no significant differences or trends in the stability data and that the proposed re-test period is acceptable.
Studies have also been performed under stress conditions in order to show the main degradation pathways. The results demonstrate that ranolazine is stable in acidic and basic conditions while in an oxidative medium two degradation products were observed.
A photostability study has also been performed in accordance to ICH requirements and the results show that the active substance is not sensitive to light.
At the time of the approval the applicant committed to continue the on-going stability studies on three commercial scale production batches of ranolazine active substance until the end of the proposed re-test period.

**Medicinal Product**

- Pharmaceutical Development

The short biological half-life of the active substance and consequently the difficulties in maintaining the desired concentrations in the blood, determined the need for the development of a prolonged release formulation. The desired prolonged-release characteristics are achieved by developing a matrix tablet, where a pH-dependent polymer (methacrylic acid-ethyl acrylate copolymer 1:1) is used that is insoluble in low pH and begins to dissolve at about pH >5. In this way, the polymer restricts the high solubility of ranolazine in acidic mediums (e.g. gastric environment) and achieves a prolonged release by dissolving in a basic environment, where ranolazine is less soluble and thus more time is needed for its release.
Since ranolazine is very slightly soluble in water several studies were conducted in order to determine the effect of the active substance particle size on the finished product performance. Different batches of active substance with varying particle size distribution were used. Based on these studies appropriate specifications have been set to ensure that any potential variability in the active substance particle size distribution will not affect the dissolution of the prolonged release dosage form.
The excipients that have been employed in the formulation development are commonly used in oral dosage forms. No excipients of animal origin have been used and most of the excipients are described in the Ph. Eur. The tablets are coated with an aesthetic film coating having a different colour for each strength. The colorants used in the film coating comply with the requirements of Directive 94/36/EC.
A standard wet granulation method has been used for the process development. Data from the development studies demonstrate that the critical process parameters have been identified and

appropriate in process controls have been set up to monitor them. Scale-up trials identified and refined the targets and ranges for the critical process parameters to be used in the proposed commercial manufacturing process.
In order to control the performance of the prolonged release formulation a discriminatory dissolution test has been developed that includes tests in 4 time points. The relevance of the selected dissolution medium and dissolution conditions has been satisfactorily been demonstrated.
Different product formulations have been used in the early studies. However bioequivalence between the clinical trial formulations and the one intended for marketing has been demonstrated.
The ranolazine prolonged release tablets are packaged either in PVC/PVdC blisters or in HDPE bottles closed with a child resistant cap containing a foam liner and foil inner seal.

- Manufacture of the Product

The manufacturing process is a standard process for these kinds of formulations and consists of the following steps: granulation, compression of the granules into tablets and film-coating of the tablets. The manufacturing process has been adequately described.
Process validation studies have been performed for the 375 mg and 500 mg tablets on three commercial scale batches. Supportive batch analysis data have also been provided from 10 batches of the 375 mg tablets and 60 batches of the 500 mg tablets manufactured at commercial scale using the validated manufacturing process.
Based on the validation and batch analysis data it can be concluded that the manufacturing process is reproducible and capable of producing consistently a finished product that complies with the acceptance criteria in the release specifications.
Process validation data have not been provided for the 750 mg tablets. This is deemed as acceptable since the composition of the 750 mg tablet is dose-proportional to those of the 375 mg and 500 mg tablets. In addition, the manufacturing process, equipment, in-process controls and product specifications are similar. Given the similarity of all tablet strengths and that the process validation for the 375 mg and 500 mg was successful, the process validation for the 750 mg tablet is not expected to differ from the validation results previously obtained.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (UV, HPLC), assay (HPLC), degradation products (HPLC), dissolution (4 time-points test), uniformity of dosage units (Ph. Eur) and microbial purity (Ph. Eur). All analytical tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 15 pilot and 2-3 commercial scale batches have been presented for each strength. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out on 3 pilot scale batches for each strength packaged both in blisters and in HPDE bottles according to the ICH requirements. Samples were stored at 25$^{o}$C/60 % RH for up to 48 months and in 40$^{o}$C/75 % RH for 6 months.
The parameters tested in the stability studies were appearance, assay degradation products dissolution, water content, friability (only tested on bottled tablets) and microbiological purity.
The results of the stability studies show that in all cases there has been no significant change in the appearance, assay or dissolution profile of the tablets. No degradation products have been detected and the friability of the tablets, when stored in HDPE bottles remains unchanged. A slight increase in water content has been observed, but it appears to level off after several months, suggesting equilibration with the environment.
Therefore it can be concluded that the stability results provided are satisfactory and support the proposed the proposed shelf life of 4 years under no special storage conditions for all tablet strengths.

**Discussion on chemical, pharmaceutical and biological aspects.**

The quality of Ranolazine prolonged release tablets is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. It is a very stable substance that is presented in the form of a racemic mixture, where both enantiomers exhibit pharmacological activity. Due to the short half-life of the active substance, a prolonged release matrix oral tablet formulation has been developed, in order to achieve the desired levels in blood. The excipients employed in the formulation are commonly used and comply with Ph. Eur. requirements. The packaging material is also commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

## 2.3 Non-clinical aspects

### Introduction

Racemic ranolazine was originally developed by Syntex Research Scotland who carried out many of the earlier non-clinical investigations in the 1980s. Pharmacology studies were also conducted at various universities and other research institutes. Reproduction toxicology was undertaken at the Syntex laboratories in Palo Alto, California, USA and genetic toxicology was undertaken by various independent contract laboratories. Ranolazine was subsequently acquired by CV Therapeutics and a considerable number of additional pharmacology and pharmacokinetic studies were undertaken together with a range of toxicology investigations on potential impurities, the genotoxic potential of ranolazine and to investigate the safety margin of the proposed marketing formulation. These included detailed investigation of the pharmacology and pharmacokinetics of the enantiomers. Some of the studies were carried out at CV Therapeutics and others were commissioned from various research institutions and contract laboratories.

Only one of the pharmacology studies (CVT303.121-P) was performed in full compliance with current standards for good laboratory practices (GLP). None of the safety pharmacology studies were GLP compliant as numerous studies were performed early in the development of ranolazine when such requirements did not apply, the Applicant provided however an adequate reassurance that the data integrity was ensured. Apart from a number of non-pivotal and supplementary studies, all pivotal toxicology studies and a portion of the pharmacokinetic are GLP-compliant.

### Pharmacology

- Primary pharmacodynamics

Ranolazine's mechanism of action is thought to be selective inhibition of late inward sodium current ($I_{Na}$) relative to peak $I_{Na}$ resulting in a decrease in intracellular $Na^+$ and $Ca^{2+}$ overload and an attenuation of the deleterious electrical and mechanical consequences of $Ca^{2+}$ overload. Inhibition of late $I_{Na}$ has been observed in a number of systems. The greatest indirect measure of the effect on peak $I_{Na}$ was a 50% inhibition of the rate of rise of Phase 0 of the action potential ($V_{max}$) at a concentration of 30 μM. Direct measurements of ranolazine's effect to reduce peak $I_{Na}$ show $IC_{50}$ values in normal dogs of 294 μM and in dogs with heart failure of 244 μM. In contrast, racemic ranolazine inhibited late $I_{Na}$, with potency as low as 5 μM, with similar results being observed with the ranolazine enantiomers. The greatest selectivity observed was in myocytes from dogs with ischemic heart failure where a ~38-fold selectivity to inhibit late $I_{Na}$ over peak $I_{Na}$ was observed. In heterologous expression models, HEK293 with SCN5A KPQ mutant sodium channels, lower selectivity of ranolazine for late vs peak $I_{Na}$ has been reported. It has also been shown that ranolazine decreases cellular $Ca^{2+}$ overload and there have been many studies that show the cardioprotective actions of ranolazine in isolated

hearts. Thus, there is substantial evidence that ranolazine exerts its primary pharmacodynamic action through inhibition of late $I_{Na}$.
Ranolazine is not thought to directly inhibit $Ca^{2+}$ overload during ischemia as it has been demonstrated to cause minimal or no inhibition of peak or late calcium channel current ($I_{Ca}$) or sodium calcium exchange current.

In the receptor screening assays, ranolazine and its R- and S-enantiomers were found to have no significant binding activity to most of the receptors and ion channels examined, except for $\alpha_1$-adrenergic receptors, $\beta_1$-adrenergic receptors, $\beta_2$-adrenergic receptors, and serotonin 5-$HT_{1A}$ and 5-$HT_2$ receptors. Studies were conducted to further characterize the binding and functional activity of ranolazine, its R- and S-enantiomers and 11 metabolites (with plasma AUC > 1% the AUC of ranolazine) at $\alpha_1$-, $\beta_1$-, and $\beta_2$-adrenergic receptors, the opioid and serotonin receptors, and L-type $Ca^{2+}$ channels. Because the AUC of the most abundant ranolazine metabolite is approximately 30%-40% that of ranolazine, the metabolites were tested in these studies at a minimal concentration of 10 μM in order to exceed the expected plasma concentration range for the most abundant metabolite at therapeutic plasma levels of ranolazine.

Ranolazine, its enantiomers, and three metabolites (RS-88390, RS-89961, and RS-88772) were shown to have moderate affinity for $\alpha_{1A}$-and $\alpha_{1B}$-adrenergic receptors. Ranolazine, its S-enantiomer, and the same three metabolites had a similar affinity for $\beta_1$-adrenergic receptors, with the R-enantiomer having no significant binding activity. The affinity of ranolazine for $\beta_2$-adrenergic receptors was slightly lower, with the S-enantiomer and metabolites RS-88390 and RS-88772 having a similar affinity as the racemate. The metabolite RS-89961 had a higher affinity for $\beta_2$-adrenergic receptors, whereas the R-enantiomer had no significant binding activity.

Ranolazine had no pharmacological or metabolic cardiac effects in non-ischemic hearts at doses that were effective in suppressing the ischemia-induced electrocardiographic changes in a canine model of reversible ischemia and improving cardiac performance in a canine model of heart failure. The enantiomers had similar anti-ischemic efficacy in a dog model. In animal experiments (dogs and baboons), ranolazine, at concentrations as low as 0.3 μM, has been shown to have anti-ischemic effects. Overall, the anti-ischemic effects of ranolazine occurred at plasma concentrations that were similar to those expected to be therapeutically effective in humans.

The anti-ischemic effects of ranolazine were not associated with significant changes in BP and HR. For example, in awake dogs, ranolazine (at steady-state concentrations in the range of ≤ 18μM) did not cause significant slowing of heart rate (HR) or lowering of arterial blood pressure (BP), and did not affect coronary blood flow, coronary vascular resistance or left ventricular (LV) contractility. These findings suggest a lack of significant inhibition by ranolazine of $\alpha_1$- or βı-adrenergic-mediated responses, or L-type $Ca^{2+}$ channel currents and dependent responses. Ranolazine has also been shown to increase cardiac performance in dogs with heart failure, induced by serial microembolizations, without affecting HR, arterial BP, LV contractility, or systemic vascular resistance. Hence, the effect of ranolazine to improve LV function in dogs with chronic heart failure cannot be explained by inhibition of $\alpha_1$- or βı-adrenergic receptor-mediated effects or $Ca^{2+}$ current-dependent effects.

The lack of negative chronotropic and hypotensive effects of ranolazine, despite demonstrated $\alpha_1$- and $\beta_1$-adrenergic antagonist activity, suggest that another effect of ranolazine, yet to be determined, counteracts the anticipated depressant effects associated with $\alpha_1$- and $\beta_1$-adrenergic receptor blockade. For example, the $\alpha_1$-adrenergic receptor antagonist activity of ranolazine could be responsible for a reflex tachycardia that counters the $\beta_1$-adrenergic-mediated slowing of the HR. However, the $\alpha_1$-adrenergic blockade by ranolazine appears not to be sufficient to decrease BP at steady-state plasma concentrations less than 18 μM. Hence, the contribution of these sympatholytic effects of ranolazine to its anti-ischemic and antianginal effects, if any, remains to be established.

Oral ranolazine (resulting in plasma concentrations ≥ 10 μM) had a detrimental effect on submaximal exercise capacity in rats with myocardial infarction. It could be attributed to the high doses used and the subsequent plasma levels that were attained, which elicits other pharmacological effects, such as

weak $Ca^{2+}$ channel and β-adrenergic blocking effects, and hence, depressing cardiac function. Consistent with this hypothesis, intraperitoneal (ip) ranolazine had a mild hypotensive effect in infarcted rats. However, at lower concentrations ranolazine increased cardiac efficiency in dogs with heart failure by increasing myocardial contractile performance without increasing myocardial oxygen consumption. These effects occurred without changes in HR, BP, myocardial blood flow, or systemic vascular resistance.

- Secondary pharmacodynamics

Receptor screening and functional assays showed that ranolazine bound to α- and β-adrenergic receptors, being an antagonist. The molecule also bound to the $5HT_{1A}$-receptor, functioning as an agonist. High concentrations of ranolazine also inhibited the postsynaptic uptake of noradrenaline and serotonin in homogenised guinea pig cerebral cortex. The receptor activity of ranolazine was classified as moderate ($EC_{50}$ values in the 2-10 μM range in various test systems) but might contribute to the side effects seen in the clinical studies (e.g., orthostatism and syncope). The S-form appeared to be the enantiomer with most receptor activity, whereas the R-form had less affinity. Several of the tested metabolites bound to adrenergic and 5HT receptors with similar or lower affinity than ranolazine; RS 88390 once again was found to have similar activity as the parent compound. Another interesting finding was opioid receptor binding; ranolazine itself had only a weak affinity to μ- and κ-receptors but two metabolites (RS 88772 and RS 88697) had a higher affinity than the parent compound. However, ranolazine had no effect on the pain threshold (tail flick) in the mouse and the opioid receptor activity of the two metabolites is unlikely to be clinically important. Therefore, no studies on dependence are considered necessary. Ranolazine does not produce the characteristic effects of drug binding to the above mentioned receptors.

- Safety pharmacology programme

The safety pharmacology programme is ambitious, especially the characterisation of ion-currents and the arrhythmogenic potential of ranolazine. Pertinent findings were that ranolazine was a CNS-depressant and that the molecule, despite inhibition of rapid delayed rectifier potassium current ($I_{Kr}$) and slowly activating cardiac potassium current ($I_{Ks}$), and a moderate prolongation of the QT-time, didn't induce Torsade de Pointes (TdP) or other arrhythmias in several *in vitro* and animal models. If anything, ranolazine was anti-arrhythmic.

- Pharmacodynamic drug interactions

One study on the effects of ranolazine on isorbide dinitrate- or sildenafil-induced changes in blood pressure and heart rate in unanaesthitised dogs was submitted during the previous Trebinex procedure. This study showed that ranolazine, at therapeutic plasma concentrations, did not alter the sustained changes in mean arterial BP and HR caused by either sildenafil or isosorbide dinitrate when used in combination with either of these drugs. These results, together with clinical interaction data, provide evidence supporting the lack of a significant haemodynamic interaction of ranolazine with long-acting nitrates and the phosphodiesterase 5 inhibitor, sildenafil, in the dog.

**Pharmacokinetics**

A comprehensive non-clinical programme of ADME studies with ranolazine, and its enantiomers and metabolites, was conducted by the former developer and the Applicant. Studies of absorption, metabolism and excretion were mainly made in mice, rats, and dogs. A few additional studies were made in hamsters (absorption, metabolism and excretion), guinea pigs (metabolism), and baboons (metabolism). Distribution of [$^{14}$C]-ranolazine was studied in pigmented and albino rats. Plasma protein binding was studied with mouse, rat, dog and human plasma, and with purified human plasma albumin and α-1 acid glycoprotein. *In vitro* metabolism was studied in liver microsomes isolated from mouse, rat, dog, and man. Pharmacokinetic drug interactions, mainly with statins, were investigated in canine MDCK-MDR1 cells and human liver microsomes *in vitro*. Finally, toxicokinetic data were collected in conjunction with several of the toxicology studies.

The analytical methods include liquid scintillation counting and whole body autoradiography for radioactivity, and HPLC with UV- and fluorescence detection for unlabeled ranolazine. More recent studies used LC/MS/MS. The analytical methods were not formally validated, which is a shortcoming. However, the Applicant provided an acceptable rationale in the previous Trebinex procedure and this shortcoming is not considered serious.

Absorption of ranolazine was rapid with $t_{max} < 1$ hour after oral administration in all studied species for both total radioactivity and ranolazine. In studies where both parameters were determined, $C_{max}$ for total radioactivity was about one order of magnitude greater than that for ranolazine, suggesting an extensive and rapid, possibly pre-systemic, metabolism. The data on gender differences are scarce; most studies were performed in male animals but in one rat-study, the AUC was three times higher in the females. Repeated daily oral administration of ranolazine in rats resulted in a dramatic increase in exposure with time, particularly in the females. However, in control animals that were given a single oral dose at various time-points during the study, a similar increase was seen. This increase in exposure may be attributed to ageing of the animals; however this has not been proven. Whether a putative ageing effect could be clinically relevant was discussed in the previous procedure, but clinical data suggests that this is unlikely.

Ranolazine or its metabolites were distributed widely, including CNS. In albino rats, the highest concentrations were found in organs associated with metabolism and excretion but also in the adrenals. The latter findings are of a particular interest because the adrenals were found to be target organs in several toxicity studies, and tumours were found in the adrenals in the rat carcinogenicity study. In pigmented rats the distribution was similar but more radioactivity was found in the pigmented skin and eyes, indicating an affinity of ranolazine or its metabolites to melanin. The clearance from pigmented tissue, particularly the eyes, was slow but the binding seems to be reversible. However, ranolazine and metabolites do not absorb light in the 290-700 nm range, making studies of photo-safety unnecessary.

No distribution studies in pregnant and lactating animals were made and it is unknown whether ranolazine or its metabolites passes the placenta and/or secreted into the breast milk of lactating animals. However, based on the general behaviour of the molecule it seems likely; in view of this a warning has been included in section 4.6. of the SPC.

Plasma protein binding was moderate and similar in man and the studied animal species.

The metabolism of ranolazine is very complex with 14 identified metabolic pathways and a multitude of metabolites, several of which were pharmacologically active. This complexity increases the risk that there are clinically important adverse effects that have not been discovered in the non-clinical and clinical testing. Such adverse events could be caused by genetic idiosyncrasies, uncommon diseases, or interaction with other pharmaceuticals or food components, making a well designed post-approval pharmacovigilance programme very important. Qualitatively, the metabolism is similar in the investigated laboratory animals and man, but there were differences in the relative importance of the metabolic pathways in different species. The metabolism is mediated by the cytochrome P450 system, with in vitro data suggesting that CYP3A4 (70-87% in man), and CYP2D6 (14-17% in man) being the active isoenzymes.

The ranolazine molecule is chemically related to the local anaesthetics, sharing the (2,6-dimethyl-phenyl)amide radical. There was concern that this similarity could mean that 2,6-dimethylaniline (DMA) or other aromatic amines are produced as a part of ranolazine metabolism, possibly with the subsequent formation of DNA-adducts. This concern lead to the submission of new data regarding DMA metabolite formation in mouse, rat, and human liver microsomal fractions and rat and human cytosol fractions, including also data obtained from plasma human samples of healthy patients administered orally with ranolazine. Although DMA formation was detected in mouse and rat samples, no DMA detectable levels in human samples have been reported.

A higher proportion of drug-related components are excreted in the urine in humans (about 70%) than in the studied animals (about 50%). However, this difference is not dramatic and is unlikely to represent an increased risk for kidney toxicity in humans.

Pharmacokinetic interactions were studied and it was found that ranolazine might compete with other P-glycoprotein substrates like HMG-CoA reductase inhibitors (statins). As expected, inhibitors of CYP3A and CYP2D6 affect the metabolism of ranolazine. These aspects are discussed more thoroughly in the clinical pharmacokinetics section.

**Toxicology**

Ranolazine was investigated in a comprehensive series of toxicology studies. Pivotal studies were made in mice (single dose), rats (single- and repeat-dose for up to 52 w) and dogs (repeat-dose for up to 52 w), with supplementary studies in the same species plus hamsters. Long-term carcinogenicity studies were performed in mice and rats, and reproductive toxicity was studied in rats and rabbits. All pivotal studies are GLP-compliant but because most of the studies were carried out by the former developer and conducted between 1984 and 1994, they were not always performed according to the current guidelines. The majority of the studies used the oral route of administration. In addition, the Applicant performed a number of studies on impurities and metabolites. These studies are more recent and are also GLP-compliant.

- Single dose toxicity

The single-dose studies indicate a minimum lethal dose for ranolazine dihydrochloride of about 250 mg/kg when given by oral gavage and more than 30 mg/kg when given iv. 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.

- Repeat dose toxicity (with toxicokinetics)

In range-finding repeat-dose dog studies, deaths occurred following a single oral dose of 150 mg/kg and following a single iv dose of 40 mg/kg. There were no deaths at 300 mg/kg in an oral mouse micronucleus study. Deaths in all species were associated with convulsions, collapse, ataxia, and subdued behaviour.

The observed effects appear to be associated with toxicity to the central nervous system (CNS) and include convulsions, ataxia, prostration, and death. The pattern is relatively consistent across studies of various types and lengths, although an increased incidence and a decreased minimal lethal dose in longer studies cannot be excluded. For rat, which is the most studied species, an oral dose up to 50 mg/kg/day rarely caused death; higher doses were lethal to some animals and deaths were also seen after ≥250 mg/kg as a single oral dose. The animals often showed clinical signs of CNS toxicity prior to death. Dogs showed similar signs, but no deaths, at 60-80 mg/kg/day; a single oral dose of 150 mg/kg was lethal to one animal. Likewise, the minimal lethal dose in the oral single-dose study in mice was 250 mg/kg and several deaths occurred in the 500 mg/kg dose-group. Finally, it must be stressed that the exposure to ranolazine in humans given therapeutic doses approaches the levels that caused mortality and severe toxicity in the animals. The NOAELs obtained for both rats and dogs are remarkably low, compared with what would be expected from the acute toxicity results. This issue resulted in a major objection in the previous procedure. It was agreed that the adverse effects were probably related to high $C_{max}$ with the immediate release formulation used in the animal studies and in response to this the Applicant agreed to conduct a 28-day repeat dose study in the dog with the clinical controlled release formulation; the aim if this study was to achieve a higher AUC, whilst limiting the $C_{max}$. A pilot study however showed that this was not feasible as severe toxicity was seen at about the same AUC as previously. At the end of the previous procedure, it was concluded that the issue could not be solved non-clinically. Consequently, the proposed clinical doses cannot be supported by the repeat-dose toxicity programme but rely on clinical data.

Other findings indicating a toxic effect of ranolazine were relatively mild and confined to the high-dose groups. Target organs appear to be the adrenals, liver and kidney. Other treatment related effects seen were a moderate effect on the haematopoiesis and changes in the plasma cholesterol and triglycerides. Neither of these findings raises any serious concerns.

- Genotoxicity

The genotoxic potential of ranolazine was investigated in a series of Ames tests, chromosome aberration and mutation test in CHO-cells *in vitro*, and the mouse micronucleus test *in* vivo. An additional micronucleus test in the rat was provided during the previous Trebinex procedure. With the exception of the mammalian chromosome aberration test *in vitro*, the genotoxicity tests were negative.

The impurity Di-Ran3-pip (RS 88778) did not show any mutagenic potential in Ames test, and when up to 5% of nine different impurities were mixed with ranolazine and given orally to rats for 28 days, there were no differences compared with the controls that were given pure ranolazine. Essentially no toxicity was observed in the latter studies though comparably low doses of ranolazine were used (20 mg/kg/day).

- Carcinogenicity

Two long-term carcinogenicity studies were done in mice and rats, respectively. The mouse study is acceptable and the findings did not suggest any obvious carcinogenic potential of ranolazine. However, the rat study raised more concerns; it had to be terminated prematurely at 21 months due poor survival, quite possibly because of the too rich food ("fat rat syndrome") commonly used in long-term studies at that time. Accordingly, the power of the rat carcinogenicity study to detect relevant tumours can be questioned. Nevertheless, statistically significant increases of several different tumour types were found in the high-dose group. Affected organs were the adrenals (cortex and medulla), thyroid, testes and skin (undifferentiated sarcoma). Particularly the adrenal cortical adenomas were worrying, as this is a rare tumour type that occurred in an organ that displayed a high uptake of ranolazine and where effects were noted in the rat 3-month toxicity study. This issue resulted in a major objection which was thoroughly discussed in the previous Trebinex procedure, remaining however unsolved.

Considering the complex metabolism of ranolazine, uncertainty whether the carcinogenic metabolite DMA or other aromatic amines are produced, and ambiguous signals concerning the adrenals, new data was requested in the present procedure to finally resolve the issue. The Applicant conducted a Comet assay on liver tissue from rats exposed to ranolazine at the same dose levels as in the rat carcinogenicity study for 3 h and 24 h. As no signs of DNA damage were seen, the results alleviate the remaining concerns about a possible genotoxic or carcinogenic effect of ranolazine or its metabolites. The data submitted by the Applicant gave additional reassurance on this issue as no detectable levels of the metabolite DMA were found in human samples even though they were detected in rat and mouse samples.

- Reproduction Toxicity

The reproductive toxicity studies were conducted according to pre-ICH standards, but covered the complete reproductive and developmental process. Corresponding segment II studies in two species (rat, rabbit) were submitted. The results indicate a possible negative effect on male fertility of ranolazine. A reduction in fertility was observed when male rats in the high dose group were mated with untreated females; this reduction remained in a second mating after 32 days recovery without treatment. Furthermore, atrophy of the testes and epididymides was observed in four of the animals. In the segment II studies, growth retardation, but no malformations, of the foetus were seen at doses that were toxic for the pregnant animals. These findings are reflected in warning against the use of ranolazine during pregnancy which can be found in section 4.6. of the SPC.

- Local tolerance

Ranolazine prolonged release formulation is intended for oral administration. There was no evidence of any significant gastrointestinal effects in any study.

**Ecotoxicity/environmental risk assessment**

The Applicant submitted a new ERA and committed to perform a complete Phase II assessment in accordance with the finalised Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) as a post-authorisation commitment.

## 2.4 Clinical aspects

**Introduction**

A previous MAA for ranolazine was submitted in 2004 and had been withdrawn at Day 180 of the previous procedure. Concerns with regard to efficacy as well as safety at that time have been addressed by the applicant by providing new studies and data.

The applicant did not seek formal scientific advice.

*The indication applied for by the applicant was:*
Latixa is indicated 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). Due to its pharmacodynamic profile, Latixa may be particularly relevant for those patients in whom a decrease in heart rate or blood pressure, or increase in PR interval is undesirable.

*The indication granted is:*
Latixa is indicated 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).

**GCP**

The individual clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Pharmacokinetics**

In total, about 50 phase I studies have been conducted to evaluate the pharmacokinetics of ranolazine. Sparse sampling has also been obtained in the target population. Different formulations have been used during drug development, immediate release (IR) capsules and tablets, and different prolonged/slow/sustained release (SR/PR) formulations. “Sustained-release (SR) tablets” were identical in formulation to “prolonged-release (PR) tablets” and were only named differently during the development. Of highest relevance where the studies conducted with the final SR tablet and supporting studies evaluating the pharmacokinetics of ranolazine after intravenous administration and oral solution. Ranolazine and metabolites in plasma were determined using LC/MS/MS methods in main PK studies. Pharmacokinetic parameters have in most studies been determined using non-compartmental models. In some studies compartmental analysis using WinNonlin was used. Population pharmacokinetics analysis and PK/PD analyses were conducted using NONMEM.

- Absorption and Bioavailability

Compared with the IR tablet, the SR tablet clearly displays a prolonged release profile with absorption rate-limited elimination. Maximum concentrations are reached on average 4-5 h after single dose administration and somewhat earlier (2-4 h) after multiple dose administration. Absolute bioavailability of the SR formulation has not been determined and is difficult to estimate from provided data. Absolute bioavailability of the IR formulation at lower doses ranged between 30 and 50%. Food does not affect the rate or extent of absorption of ranolazine from the SR formulation. There were no signs of dose dumping.

During drug development, the manufacturer of drug substance and drug product has been changed. The final product produced by DSM has a more rapid rate of absorption but the same extent of absorption as the Syntex tablets used in earlier PK studies and in clinical study CVT 3031. This is considered of limited clinical relevance, especially since the DSM product was used in the pivotal clinical trial CVT 3033 and study CVT 3037.

- Distribution

Volume of distribution ($V_{ss}$) was estimated at about 180 l. The protein binding is approximately 62%, with a higher affinity to $\alpha$-1 acid glycoprotein than to albumin. The protein binding of the metabolites CVT-2514, CVT-4786, and CVT-2537 is about 73-79%, and the protein binding of CVT-2738 is about 15%. Ranolazine distributes partially to blood cells. The blood/plasma ratio was in the range of 0.62-0.88.

- Elimination

Ranolazine is eliminated by metabolism to a large number of metabolites. Less than 5-6% of the dose is eliminated unchanged in urine.The elimination half-life after intravenous infusion was 2-3 h. Elimination half-life at steady state after oral administration of Latixa SR tablets was about 7 h due to the absorption rate-limited elimination. Ranolazine displays moderately non-linear pharmacokinetics. At steady state plasma concentrations obtained with 500 to 1000 mg b.i.d., ranolazine CL was predicted to be in the range 27-35 l/h. Ranolazine is a racemate. The pharmacokinetics of the individual enantiomers is similar. There is no interconversion between (+) R and (-) S ranolazine.

In the mass balance study, 73% of the dose was excreted in urine and 24% in faeces. Total recovery was 97.6%. The elimination half-life of radioactivity was on average 41 h. Fourteen primary metabolism pathways have been identified, four of which seem to be the major ones, with N-dealkylation at the N4 position of piperazine ring, O-demethylation of the methoxy group on the methoxyphenyl ring being the two most important pathways. Over 100 metabolites were detected in urine and 48 metabolites in plasma. The main primary metabolites in plasma are CVT-2738, CVT-4786, CVT-2514, CVT 2512 and ranolazine glucuronide. The 25 metabolites quantified in urine account for 65% of the radioactivity excreted in urine and for about 50% of the administered dose. The sum of AUCs of the quantified metabolites and ranolazine accounted for 49% of the AUC for radioactivity in plasma, with ranolazine accounting for 13%. In faeces, 25 metabolites were identified, but quantification of metabolites was not performed. Hence, about 50% of the administered dose and plasma radioactivity have not been fully characterised. However, radiochromatograms of plasma and urine suggest that metabolites not quantified are all minor metabolites and radiochromatograms of faeces clearly suggest that CVT 2512 is the major metabolite in faeces. Hence, given the complex metabolic profile of ranolazine, the characterisation of the elimination is considered sufficient. It seems reasonable to conclude that a large number of minor metabolites constitute the remaining radioactivity.

CYP3A4 is the major catalysing enzyme, with contribution of CYP2D6. Available data suggest that CVT 2738 formation is mainly mediated by CYP3A4, CVT 2514 is primarily dependent on CYP2D6 and formation of CVT 2512 is dependent on both CYP3A4 and CYP2D6. At 500 mg b.i.d. Patients deficient of CYP2D6 metabolising capacity (PMs) had 62% higher ranolazine AUC than patients with

extensive CYP2D6 metabolising capacity (EMs). The corresponding difference at the 1000 mg b.i.d. dose was 25%.

The only metabolites with possibility to contribute to the effect are CVT 2514 and CVT-2738. The unbound concentration of CVT 2514 is about 20% of that of ranolazine with a similar AUC-ratio metabolite/ranolazine in different populations (renal impairment, hepatic impairment or during concomitant medication with CYP3A4 inhibitors). Hence, CVT 2514 is expected to contribute to a limited extent to efficacy. In patients with normal renal function the unbound AUC of CVT-2738 is about 60% of that of ranolazine. In severe renal impairment the exposure of CVT-2738 is increased almost 5-fold resulting in higher unbound AUC than for ranolazine. Hence, CVT-2738 may contribute to the effect, especially in patients with reduced renal function.

- Dose proportionality and time dependencies

Ranolazine displays moderately non-linear pharmacokinetics. AUC and $C_{max}$ increase slightly more than in proportion to the increased dose after single dose oral administration of Latixa. At steady-state the nonlinearity is more pronounced. After single dose administration, the increases in AUC were 23% and 53% higher than the corresponding increases in dose from 500 mg to 1,000 mg and 1,500 mg, respectively. The corresponding figures at steady-state were 72% and 152%. Steady state exposures were 42, 56 and 66% higher than predicted from single dose data at 500, 1,000 and 1,500 mg *b.i.d*, respectively. After intravenous administration, the ranolazine plasma profile was modelled by a two-compartment model with a combination of one linear and one saturable elimination pathway. Modelling of PK suggests that the non-linear elimination pathway accounts for between 30 and 50% of the elimination. The non-linearity was more pronounced in CYP2D6 EMs than in PMs. These results suggest that part of the non-linearity is a saturation of the CYP2D6 elimination pathway and that another parallel pathway is also saturable.

- Variability

Both inter- and intraindividual variability in ranolazine pharmacokinetics is large after oral administration of the SR formulation. The intra-subject variability after intravenous infusion was estimated to 18% and to 32% in phase I studies and 42% in phase II studies after administration of the SR formulation. Inter-individual variability in AUC was about 50%, in $C_{max}$ about 40% and in $C_{min}$ about 70% after administration of Latixa 1000 mg bid.

- Special populations

The influence of renal or hepatic impairment have been evaluated in separate phase I studies. A population pharmacokinetic analysis evaluating the influence of weight, creatinine clearance and/or age, CHF, diabetes, concomitant administration of diltiazem, atenolol, amlodipine and digoxin on clearance parameters; effects of weight, creatinine clearance and/or age, CHF, diabetes on volume; formulation and food effect on absorption rate has been conducted.

In the renal impairment study, the influence of renal impairment on ranolazine pharmacokinetics was unexpectedly high with mean AUC 75, 71 and 99% higher in the mild, moderate and severe RI groups, respectively, compared to the control group. The variability in ranolazine exposure was high in subjects with renal impairment. Already in subjects with mild renal impairment, the exposure ranged from similar to that in normal renal function up to 4-fold higher. Also in severe renal impairment, the variability was high with a similar range in exposure as in mild renal impairment. The effect of dialysis on the pharmacokinetics of ranolazine has not been studied. Some of the metabolites displayed large increases in exposure (up to 10-fold) with decreased renal function. Exposure to the active metabolite CVT-2738 increased almost 5 fold resulting in an unbound exposure exceeding that of ranolazine in patients with severe renal impairment. The terminal half-life was prolonged and steady state was not reached. Hence, a larger increase in exposure is expected at steady state. This metabolite may clearly contribute to the effect in patients with reduced renal function. If similar distribution to active sites is assumed and the unbound exposure active moieties (ranolazine + CVT-

2738) calculated, the unbound exposure of active moiety will be increased approximately 1.8-fold, 2.5-fold, 3-fold in mild, moderate and severe renal impairment, respectively.

In study CVT-3036 (MERLIN-TIMI 36), many of the concentration-related adverse events were clearly increased with decreased renal function. The frequency of nausea is clearly related to renal function and is 8, 13 and 23% in patients with CLcr >60, 30-60 and <30 ml/min, respectively. Based on these data cautious titration of the dose is recommended in patients with renal impairment. This increase in adverse events in severe renal impairment was obtained although these patients received only 500 mg bid (i.e. a dose reduction of 50%). Also, the distribution of renal function in the severe group is not known. It is likely that the group mainly contains patients with creatinine clearance >20 ml/min and that patients with lower creatinine clearance are poorly represented. The population model predicts considerable increase in exposure as creatinine clearance is reduced below 20 ml/min. The exposure to the active metabolite is also very variable in severe renal impairment. With an on average 5-fold increase in AUC in severe renal impairment, considerably higher exposure is expected in patients with very poor renal function. A larger increase in adverse events would be expected in these patients. For these reasons use in patients with severe renal impairment is contraindicated in section 4.3 of the SPC, and caution advised in mild to moderate impairment in section 4.4, with additional information in SPC section 4.2.

Mild hepatic impairment did not affect the pharmacokinetics of ranolazine. In moderate hepatic impairment $AUC_{0-12}$ was increased by approximately 75%. There are no data in severe hepatic impairment. QT prolongation was observed both in mild and moderate hepatic impairment. Based on the limited clinical data, the risk for QT prolongation and the increased ranolazine exposure, use in patients with moderate to severe hepatic impairment has been contraindicated in the SPC in section 4.3. From a pharmacokinetic perspective there is no need for specific precautions in mild hepatic impairment. However, given the risk for QT prolongation, caution is advised in mild hepatic impairment in section 4.4, with additional information in SPC section 4.2.

The population analysis identified weight, renal function, NYHA class and concomitant administration of diltiazem as factors affecting ranolazine clearance. Diabetes and age had no clinically significant effect on AUC and it is stated that race and sex did not affect ranolazine PK. Exposure for a 40 kg and a 120 kg patient was, respectively, 41% higher and 27% lower than for a typical 70 kg subject. NYHA Class III or IV increased exposure by 34%. Concomitant administration of diltiazem increased exposure by 38%. Exposure for subjects with calculated normalized creatinine clearance representing the various renal impairment categories (65, 40, 20 and 10 mL/min/1.73m$^2$) was 2% (mild), 19% (moderate), 48% (severe), and 84% (very severe) higher, respectively, than for subjects with normal creatinine clearance. The effects of covariates on $C_{max}$ and AUC and steady state concentration time profiles for different sub-groups as well as the dependency of exposure on several risk factors combined was presented. However, EM/PM status, which is an important factor for ranolazine exposure, has not been included as covariates in the analysis. Also, the effect of diltiazem on ranolazine clearance estimated in the population model is low compared to the conducted interaction studies. Hence, the diltiazem effect may to be underestimated. Sex and race were not included as covariates in the model. Hence, no conclusions can be drawn regarding these factors. However, other data overall suggest that gender does not seem to have a clinically relevant influence on ranolazine pharmacokinetics.

- Pharmacokinetic interaction studies

In vitro studies indicate that ranolazine and the metabolites RS-94287 and RS-88390 have low potential to inhibit the metabolism of substrates of CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4. The potential for ranolazine to inhibit CYP2B6 has not been evaluated.

Concomitant administration of CYP3A4 inhibitors results in large increases in ranolazine exposure; 3 to 4-fold increase with a potent CYP3A4 inhibitor (ketoconazole) and 2.4-fold increase with a moderate CYP3A4 inhibior (diltiazem). Potent CYP3A4 inhibitors have therefore been contraindicated in the SPC (section 4.3, 4.5) and cautious titration of the dose is recommended during concomitant use with moderate CYP3A4 inhibitors (SPC section 4.2).

Potent CYP3A4 induction caused a major decrease (95%) in ranolazine exposure. Therefore, Latixa should not be co-administered with inducers of CYP3A4. This is stated in sections 4.4 and 4.5 of the SPC.

The pharmacokinetics of ranolazine in CYP2D6 EMs and PMs with and without concomitant administration of the moderate CYP3A4 inhibitor diltiazem was evaluated in a specific drug-drug interaction study. During concomitant administration of diltiazem 180 mg bid and ranolazine 500 mg bid ranolazine AUC was increased 2.4-fold in EMs and 2.1-fold in PMs. The AUC in a PM at ranolazine 500 mg with diltiazem was 3.4 fold higher than the AUC of an EM at 500 mg without diltiazem. In both EMs and PMs several subjects withdrew due to adverse events or long PR interval. The number of subjects reporting adverse events (AEs) was high (80–100%) in PMs regardless of diltiazem treatment and in EMs on diltiazem. The EM group receiving ranolazine alone reported fewer AEs (RAN 500 mg bid [42%], RAN 1000 mg bid [67%]). Appropriate recommendations for moderate CYP3A4 inhibitors are discussed below (see *Combination of risk factors).*

Potent inhibition of CYP2D6 (by paroxetine) resulted in a 24% increase in AUC after administration of ranolazine 1,000 mg *b.i.d*. At the dose level 500 mg *b.i.d*, potent CYP2D6 inhibition is estimated to result in an increase in ranolazine AUC of about 60%, which is said to be within a well tolerated range. Section 4.5 of the SPC has been amended with this information.

Ranolazine is a substrate and a moderate inhibitor of P-gp. Verapamil increased ranolazine AUC with 125%. The mechanism is postulated to be P-gp inhibition in the gut, increasing the bioavailability of ranolazine. However, data from study 3112 where verapamil decreased clearance of intravenously administered ranolazine suggests that the interaction in part is caused by CYP3A4 inhibition. Appropriate recommendations for co-administration with P-gp inhibitors are discussed below (see *Combination of risk factors).*

Ranolazine increased digoxin AUC with 60% and decreased digoxin $CL_R$ by 14%. It seems likely that the mechanism of interaction, as proposed by the applicant, is inhibition of P-gp both at the levels of intestinal absorption and renal tubular excretion of digoxin. The increased digoxin exposure is moderate, but during P-gp inhibition plasma levels may be moderately increased while the increased distribution to tissues, *e.g.* CNS, may be considerably larger. Ranolazine 1,000mg *b.i.d.*, has a similar effect on digoxin oral clearance as verapamil. Ranolazine is, thus, a moderate to potent P-gp inhibitor.

Ranolazine inhibited simvastatin transport *in vitro* and increased the plasma concentrations of simvastatin and simvastatin acid *in vivo* (60 and 39%, respectively). The mechanism of interaction could be partly P-gp inhibition, partly CYP3A4 inhibition. Either way, the extent of interaction was fairly small, and it can be concluded that ranolazine is at most a mild inhibitor of CYP3A4.

Ranolazine did not affect the pharmacokinetics of warfarin but caused a statistically significant, but clinically not meaningful effect on maximum prothrombin time. The study was conducted with ranolazine IR 400 mg HCl *t.i.d*. and although firm conclusions cannot be drawn from these data they strongly suggest that ranolazine SR at the therapeutic dose range is unlikely to have a significant effect on warfarin PK.

The nonlinearity in ranolazine clearance is at least partly caused by autoinhibition of CYP2D6. In study CVT301-13 the dextromethorphan/dextrorphan ratio of increased from 0.00674 to 0.05674 during 4 days administration of ranolazine, indicating that a partial inhibition of CYP2D6 had occurred, i.e. that ranolazine is a weak CYP2D6 inhibitor. It is however, unclear if the effect of ranolazine on CYP2D6 would result in clinically relevant changes in exposure of concomitantly administered CYP2D6 substrates. The applicant has committed to evaluate the effect of ranolazine on a sensitive CYP2D6 substrate, e.g. metoprolol.

- Combination of risk factors

Ranolazine exposure is increased in patients with concomitant administration of CYP3A4 inhibitors, P-gp inhibitors, CYP2D6 inhibitors, patients with renal impairment, patients with hepatic impairment and patients with CYP2D6 poor metaboliser (PM) status. Exposure is also higher in patients in the lower weight range and in the elderly. In patients with two or more of these factors ranolazine exposure might become very high.

Earlier studies have clearly demonstrated a concentration-related incidence of adverse events including CNS related adverse events. The safety of different sub-groups was evaluated in study CVT-3036. However, this discussion only accounts for the risk factors separately and does not address patients with several risk factors.

Based on the pharmacokinetic and safety evaluation there is a need for 375 mg as initial dose in several sub-groups and a need for careful titration in additional sub-groups. In order not to complicate the SPC, and to reduce the risk of initiation at a too high dose in some groups, the SPC recommends 375 mg bid as the initial dose in all patients, with subsequent dose titration to 500 and 750 mg based on patient's response (section 4.2 of the SPC). In addition, a strong warning for a combination of risk factors has been included in section 4.4.

**Pharmacodynamics**

Currently available anti-anginal drugs either decrease oxygen needs by reducing haemodynamic factors such as heart rate, blood pressure or inotropic state, or increase oxygen supply by coronary vasodilatation. Ranolazine alters the relationship between cardiac work and myocardial oxygen consumption by inhibiting a number of ion channels, especially the late $I_{Na}$ channel and this is regarded as the main target for effect. The inhibition of the late sodium channel causes a reduction in the oxygen requirements and makes the heart generate the same work with less oxygen consumption. It also attenuates the myocardial sodium overload and, subsequently, the intracellular calcium overload, which is a crucial factor for the development of myocardial ischaemia leading eventually to cell death. Ranolazine also binds to α1a, b and β1,2-adrenergic receptors with affinities (Ki values) in the range of 5 to 20 μM, and to serotonin 5HT1A receptors with an affinity of 2 μM. Ranolazine can be expected to attenuate α1- and β1-adrenergic receptor-mediated responses, and to have 5HT1A receptor agonist activity over this concentration range.

- Mechanism of action, Primary and Secondary pharmacology

The knowledge regarding the mode of action of ranolazine originates mainly from pre-clinical studies (see above). The same mode of action is probably operative in humans as well.

The anti-ischemic effects, of ranolazine are achieved without a concomitant effect on heart rate, arterial blood pressure, LV contractility, or vasodilation. The contributions of α1- and β1-adrenergic receptor blocking effects, although not specifically investigated in humans, do not appear to be clinically significant at recommended doses.

With regard to knowledge of relative contribution of the different mode-of-actions in humans, such lack of detailed data was considered acceptable concerning clinical efficacy and safety.

*PK/PD modelling*
A population pharmacokinetic-pharmacodynamic (PK/PD) evaluation of the effect of ranolazine on exercise treadmill time (ETT) has been performed. The drug related effect on ETT, excluding the placebo (learning) effect, increased linearly with the ranolazine plasma concentration with an average slope of 16.8 sec for each increase by 1,000ng/mL in males, and 6.4 sec for each increase by 1,000ng/mL in females. The factors age, weight, race, CHF classified as NYHA I–II, diabetes, concomitant anti-anginal medication, and drug formulation (IR or SR) had no effect on the slope.

**Clinical efficacy**

Initially in the development programme, an immediate release formulation was used, but subsequently a prolonged release formulation was developed and used in later clinical trials. Furthermore, the doses have increased considerably in later trials compared to earlier and the dosing intervals have become less frequent with the use of the SR formulation, from 4 times daily to twice daily.

Table 1 summarises the efficacy and safety studies that are included in the application. Studies beginning with RAN were phase II studies done with the immediate release formulation. All CVT studies were performed with the prolonged release formulation, which marketing authorisation is applied for.
In addition to these studies, study CVT 3023, which specifically evaluated the tolerability of ranolazine at higher doses, was included in the application.
Data of study CVT 3036 (MERLIN) was provided by the applicant during the evaluation at day 121 of the procedure, to alleviate concerns raised by the CHMP in the day 120 list of questions. This study included 6560 patients, of which 3268 received Latixa.

**Table 1**

| Study (Formulation) | Patients Randomized | Patients Included In Primary Efficacy Analyses | Ranolazine[a] | | Placebo |
|---|---|---|---|---|---|
| | | | < 240mg | ≥ 240mg | |
| **Phase 3 Studies (PR)** | | | | | |
| **CVT 3033** | 823 | 791 | 0 | 554 | 269 |
| **CVT 3037** | 565 | 558 | 0 | 281 | 284 |
| **CVT 3031[b]** | 191 | 175 | 0 | 191 | 179 |
| **Subtotal** | 1,579 | 1,524 | 0 | 1,026 | 732 |
| **Other Controlled Studies Demonstrating Efficacy (IR)** | | | | | |
| **RAN072[b]** | 106 | 104 | 79 | 27 | 106 |
| **RAN080[b]** | 158 | 153 | 0 | 155 | 154 |
| **RAN1514[b]** | 318 | 312 | 0 | 315 | 310 |
| **Subtotal** | 582 | 569 | 79 | 497 | 570 |
| **Total** | **2,161** | **2,093** | **79** | **1,602** | **1,302** |

IR = immediate-release; PR = prolonged-released.
a Ranolazine free base (PR) molecular weight=427.54 and ranolazine dihydrochloride (IR) molecular weight=500.48
b Crossover study

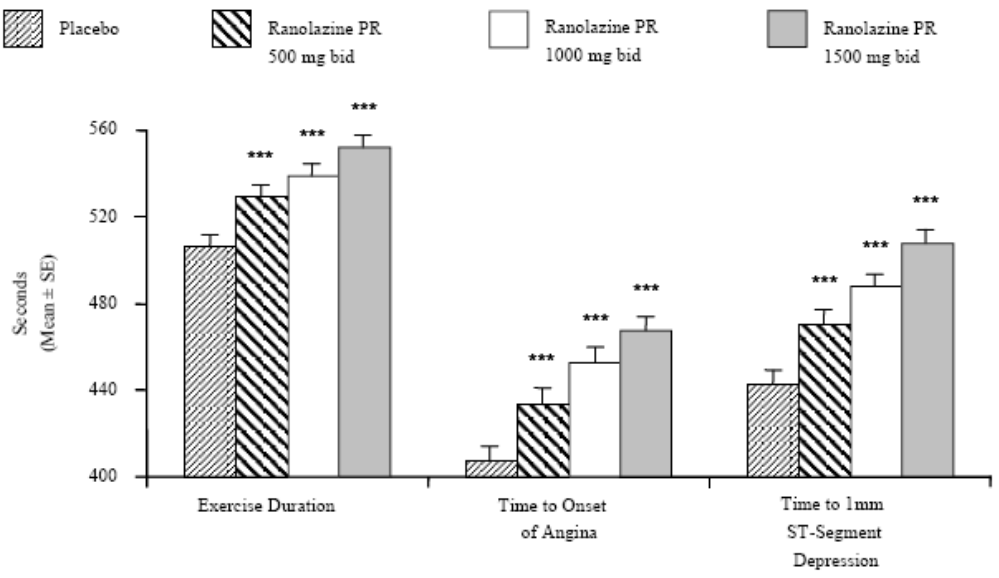
- Dose-response studies

The main dose-response study is CVT 3031. It was a double-blind, randomised, placebo-controlled, 4-period cross-over study enrolling 191 patients with stable angina pectoris treated with 500, 1000 and 1500 mg ranolazine bid against placebo. Treatment duration was, however, only one week at each dose level. The primary objective of this study was to determine the effect of ranolazine SR monotherapy compared to placebo in patients with chronic stable angina on exercise treadmill test (ETT) duration at the time of trough ranolazine plasma levels (12 hours post-dose). Some of the secondary objectives were to determine the effect at trough on time to onset of angina, and time to 1 mm ST-segment depression of the 3 doses of ranolazine SR monotherapy compared to placebo. Sublingual nitroglycerin tablets were to be used only as a treatment for acute angina (but not within 60 minutes of the ETT), but anti-anginal medications (long-acting nitrates, beta blockers, and calcium channel blockers) were prohibited for 48 hours prior to Visit 1 and throughout the trial.

Improvement of exercise duration was statistically significant compared to placebo for all three doses of ranolazine. The mean difference compared to placebo were 23.8 seconds (500 mg bid), 33.7 seconds (1000 mg bid), and 45.9 seconds (1500 mg bid), showing a clear dose-response pattern; in addition, there was a statistically significant effect with regard to some secondary outcome parameters

(see figure below). The positive results in the efficacy endpoints at trough were similarly observed for the same endpoints at peak concentrations of ranolazine.

**Figure 1 - Key Efficacy Endpoints at Trough – Study CVT 3031 (All/Near Completers)**




***p ≤ 0.001 vs placebo

PR = prolonged-release; SE = standard error; bid = twice daily

However, most patients discontinued the study prematurely while on the 1500 mg dose (13/187 patients, 7%). Rates of withdrawal from the other treatments were: placebo 3/179 patients, 2%; 500 mg 6/181, 3%; 1000 mg 1/180, 1%. Most who withdrew because of adverse events (AEs) were also receiving the 1500 mg dose. The rate of withdrawals because of an AE was: 1500 mg, 11/187 patients, 6%; 1000 mg, 1/180 patients, 1%; 500 mg 1/181 patients, 1%; and placebo, 2/179 patients, 1%. Therefore, the disproportional increase in adverse events on the 1500 mg bid dose led to the conclusion that doses above 1000 mg bid could not be used.

- The main clinical study

Study CVT 3033

Study CVT 3033 was an add-on study, in which ranolazine in two doses (750 mg bid and 1000 mg bid) were added to atenolol, amlodipine or diltiazem. The base-line drugs and their respective doses were chosen based on data regarding angina pectoris treatment in five European countries and these drugs were the most commonly used and the chosen doses the most commonly prescribed.

Methods

Study participants
All patients had had chronic stable angina for at least 3 months. The pre-qualifying exercise test had to be symptom-limited and show the usual definite signs of myocardial ischaemia during exercise (0.1mV ST segment depression). Mean age of included patients was 64 years. The majority was Caucasians. Only about 23% were females (table 2). Twenty-three percent were diabetics and 29% had diagnosed of congestive heart failure. Over 60% were hypertensives and 58% had had a previous myocardial infarction (table 3). Few patients were 75 years or older, in the Integrated Safety Database these elderly patients accounted for only about 6-7% of the studied subjects. The study population was considered to be sufficiently representative for a broad European population with stable angina.

**Table 2 - Summary of demographic data. Study CVT 3033**

| | Ranolazine SR | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **750mg *b.i.d.* N=279** | **1,000mg *b.i.d.* N=275** | **Placebo N=269** | **Total N=823** | **p-Value** |
| **Mean age, years** | 64.3 | 63.9 | 63.7 | 64.0 | |
| **Age category, n(%)** | | | | | |
| < 65 years | 141 (50.5) | 138 (50.2) | 129 (48.0) | 408 (49.6) | |
| ≥ 65 years | 138 (49.5) | 137 (49.8) | 140 (52.0) | 415 (50.4) | ns |
| **Gender, n(%)** | | | | | |
| Male | 217 (77.8) | 219 (79.6) | 202 (75.1) | 638 (77.5) | |
| Female | 62 (22.2) | 56 (20.4) | 67 (24.9) | 185 (22.5) | ns |
| **Race, n(%)** | | | | | |
| Caucasian | 269 (96.4) | 269 (97.8) | 265 (98.5) | 803 (97.6) | ns |
| Non-caucasian | 10 (3.6) | 6 (2.2) | 4 (1.5) | 20 (2.4) | |

**Table 3 - Summary of pre-existing cardiovascular conditions. Study CVT 3033**

| | Ranolazine SR | | | | |
|---|---|---|---|---|---|
| **Pre-existing condition** | **750mg *b.i.d.* N=279 n (%)** | **1,000mg *b.i.d.* N=275 n (%)** | **Placebo N=269 n (%)** | **Total N=823 n (%)** | **p-Value** |
| Hypertension | 177 (63.4) | 177 (64.4) | 173 (64.3) | 527 (64.0) | ns |
| Prior MI | 166 (59.5) | 158 (57.5) | 150 (55.8) | 474 (57.6) | ns |
| CHF | 87 (31.2) | 78 (28.4) | 77 (28.6) | 242 (29.4) | ns |
| Prior CABG | 53 (19.0) | 56 (20.4) | 36 (13.4) | 145 (17.6) | ns |
| Prior PTCA | 46 (16.5) | 53 (19.3) | 53 (19.7) | 152 (18.5) | ns |
| Ventricular arrhythmia | 25 (9.0) | 27 (9.8) | 19 (7.1) | 71 (8.6) | ns |
| Intermittent claudication | 23 (8.2) | 20 (7.3) | 19 (7.1) | 62 (7.5) | ns |
| Atrial arrhythmia | 22 (7.9) | 23 (8.4) | 20 (7.4) | 65 (7.9) | ns |
| Stroke | 15 (5.4) | 15 (5.5) | 11 (4.1) | 41 (5.0) | ns |
| Cardiac arrest | 6 (2.2) | 1 (0.4) | 6 (2.2) | 13 (1.6) | ns |
| Pulmonary embolism | 4 (1.4) | 1 (0.4) | 2 (0.7) | 7 (0.9) | ns |

CHF = congestive heart failure; CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Treatments

Eight hundred and twenty-three patients were randomised to either ranolazine 750 mg bid. (n=279), ranolazine 1000 mg bid. (n=275) or placebo (n=269) as add-on treatment to atenolol 50 mg od (n=236), amlodipine 5 mg od (n=175), or diltiazem 180 mg od (n=143).

Outcomes and Endpoints

The objectives was to determine the effects of ranolazine at doses of 750 mg bid or 1000 mg bid compared to placebo on symptom-limited exercise duration among patients with chronic stable angina treated with commonly used approved anti-anginal drugs. The primary efficacy end point was the change from baseline in exercise duration at trough after 12 weeks on study drugs using LOCF for imputation of missing data.

Results

At baseline there were no differences between the three treatment arms, all showed exercise duration of approximately 7 minutes. Since one requirement was the ability to perform an exercise test with a duration of 3 to 9 minutes (modified Bruce protocol) this result could be expected (table 2). The mean increases in exercise duration at trough were statistically significantly greater for patients treated with

either dose of ranolazine SR than with placebo (table 4). There was, however, no difference between the two doses of ranolazine (table 5).

**Table 4 - Mean Change from Baseline in ETT Duration (s) at Trough Levels of Placebo, Ranolazine 750 mg bid, and Ranolazine 1000 mg bid: ITT Population**

| | Timepoint | Statistic | Placebo | Ranolazine SR 750 mg | Ranolazine SR 1000 mg |
|---|---|---|---|---|---|
| Baseline | Week 0 | Mean<br>SE<br>Range<br>N | 418.3<br>6.3<br>184, 561<br>258 | 416.4<br>6.2<br>188, 539<br>272 | 414.7<br>6.3<br>198, 540<br>261 |
| Change from Baseline | Week 2 | Mean<br>SE<br>Range<br>N | 54.6<br>5.4<br>-147,359<br>258 | 88.7<br>6.9<br>-312,442<br>272 | 92.5<br>6.3<br>-187,409<br>261 |
| | Week 6 | Mean<br>SE<br>Range<br>N | 84.7<br>7.1<br>-244, 467<br>252 | 114.0<br>7.7<br>-221,486<br>263 | 116.4<br>8.0<br>-235,452<br>245 |
| | Week 12 | Mean<br>SE<br>Range<br>N | 92.3<br>8.0<br>-240, 527<br>244 | 119.4<br>8.5<br>-276,516<br>254 | 117.6<br>7.7<br>-253,448<br>239 |
| | Week 12 LOCF | LS Mean<br>SE (LS Mean)<br>Range<br>N | 91.7<br>8.3<br>-240, 527<br>258 | 115.4<br>8.0<br>-276,516<br>272 | 115.8<br>8.2<br>-253,448<br>261 |

**Table 5 - Change from Baseline in ETT Duration (s) at Trough Levels of Ranolazine vs. Placebo at Week 12 (LOCF). Differences from ANCOVA: ITT Population.**

| | Treatment | | |
|---|---|---|---|
| | Ranolazine SR 750 mg vs Placebo | Ranolazine SR 1000 mg vs Placebo | Average of the ranolazine SR dose groups vs placebo |
| Mean Difference | 23.7 | 24.0 | 23.9 |
| SE | 10.9 | 11.0 | 9.5 |
| 95% CI | (2.3, 45.1) | (2.4, 45.7) | (5.2, 42.6) |
| P-value | 0.030 | 0.029 | 0.012 |

The effects on exercise duration were statistically significant. However, the base-line treatment in CVT 3033 was not optimised, which created an uncertainty about the importance of the shown change and therefore the Applicant submitted a post hoc subgroup analysis in the so called maximally dosed patients (249 patients). A patient with angina, a heart rate ≤60 beats/minute, a systolic blood pressure ≤100 mg Hg and/or an ECG PR interval ≥200 msec would, according to the Applicant, cause the clinician to exercise considerable caution in initiating or increasing the dose of an anti-anginal drug, having significant haemodynamic effects or an effect on AV node conduction. The patient may be considered, on clinical grounds, to be "maximally dosed". In study CVT 3033, approximately one third of patients (n=249) fell into this category.

**Table 6 - Exercise performance by *"maximally dosed patients"***

| | **Placebo** | | **Ranolazine 750 mg *b.i.d.*** | | **Ranolazine 1000 mg *b.i.d.*** | |
|---|---|---|---|---|---|---|
| | **Subgroup** | | **Subgroup** | | **Subgroup** | |
| | **MD** | **Other** | **MD** | **Other** | **MD** | **Other** |
| **Change from Baseline in Duration of Exercise at Trough, sec** | | | | | | |
| N | 79 | 179 | 88 | 184 | 82 | 179 |
| Lease Squares Mean ± SE | 90.8±14.5 | 92.2±9.8 | 125.0±13.8 | 110.8±9.6 | 125.6±14.1 | 111.2±9.8 |
| RAN vs. Placebo Treatment Difference ± SE | -- | -- | 34.2±19.5 | 18.6±13.2 | 34.8±19.9 | 19.0±13.3 |
| RAN vs. Placebo Treatment Difference p-value | -- | -- | 0.0803 | 0.1601 | 0.0800 | 0.1538 |
| ***Treatment by subgroup interaction p-value = 0.7509*** | | | | | | |
| **Change from Baseline in Time to Onset of Angina at Trough, sec** | | | | | | |
| N | 79 | 179 | 88 | 184 | 82 | 179 |
| Lease Squares Mean ± SE | 116.6±16.1 | 113.3±10.8 | 152.7±15.4 | 139.8±10.7 | 149.6±15.7 | 135.9±10.9 |
| RAN vs. Placebo Treatment Difference ± SE | -- | -- | 36.1±21.6 | 26.5 14.7 | 33.0±22.0 | 22.6± 4.7 |
| RAN vs. Placebo Treatment Difference p-value | -- | -- | 0.0953 | 0.0715 | 0.1336 | 0.1253 |
| ***Treatment by subgroup interaction p-value = 0.9089*** | | | | | | |
| **Change from Baseline in Time to 1-mm ST-Segment Depression at Trough, sec** | | | | | | |
| N | 76 | 171 | 84 | 176 | 79 | 165 |
| Lease Squares Mean ± SE | 128.3±16.2 | 123.6±10.9 | 137.6±15.6 | 148.6±10.8 | 148.6±15.8 | 145.0±11.2 |
| RAN vs. Placebo Treatment Difference ± SE | -- | -- | 9.4±21.9 | 24.9±14.9 | 20.3±22.2 | 21.4±15.1 |
| RAN vs. Placebo Treatment Difference p-value | -- | -- | 0.6689 | 0.0940 | 0.3600 | 0.1575 |
| ***Treatment by subgroup interaction p-value = 0.8033*** | | | | | | |

MD = "maximally dosed"

The "maximally dosed" group, however, showed similar results as the whole studied population, in fact the exercise duration was slightly longer and therefore it is concluded that beneficial effects of ranolazine have been shown although the effects can be regarded as modest. The results in this subgroup imply that an effect also in a "state-of-the-art" treated population could be expected.

**Study CVT 3037**

In a supportive study (CVT 3037), ranolazine was studied in 565 patients over 6 weeks. In this study, patients reporting an average weekly rate of ≥3 angina attacks were randomised to receive ranolazine 500 mg b.i.d. or placebo for one week, followed by ranolazine 1,000mg b.i.d. or placebo for 6 weeks in addition to the maximum licensed dose of amlodipine, 10mg daily, which they had been receiving

for at least 2 weeks prior to the start of the study. In addition to treatment with amlodipine, 129/277 (47%) of patients on ranolazine and 122/281 (43%) of patients on placebo were receiving long-acting nitrates (LAN). The study randomised 565 patients and the primary efficacy measure was the average weekly rate of angina attacks during the 6 week double-blind treatment phase.

The summary statistics used to describe the treatment effect on angina attack rates in this study include a trimmed mean, computed as the average of all observations up to the 98$^{th}$ percentile, in addition to the medium, the 25$^{th}$ and 75$^{th}$ percentiles and the conventional mean. The trimmed mean was added to the analysis plan before data lock when a few patients with unusually high rates of angina attacks were observed during the blinded data review.

**Table 7 - Average Weekly Rate of Angina Attacks during the 6-Week Double-Blind Treatment Phase – Study CVT 3037**

| Average weekly rate of angina attacks (no./week) | Treatment: Placebo (n=281) | Treatment: Ranolazine (n=277) | P-value* |
|---|---|---|---|
| n | 281 | 277 | .028 (CMH) |
| Trimmed Mean (SEM) | 3.24 (0.21) | 2.82 (0.19) | |
| Median | 2.43 | 2.18 | |
| 25th Percentile - 75th Percentile | 1.47 - 4.17 | 1.24 - 3.66 | |
| Min - Max | 0.00 - 160.26 | 0.00 - 47.33 | |
| Mean (SEM) | 4.30 ( 0.64) | 3.29 ( 0.26) | |

Note: * CMH = Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center
Note: Trimmed mean is calculated including data up to the 98th percentile within each of the treatment groups.

**Table 8 - Average Weekly Rate of Angina Attacks During the 6-Week Double-blind Treatment by Concomitant Use of LANs – Study CVT 3037**

| Average Weekly Rate of Angina Attacks (no./week) | Treatment: Placebo (n = 281) | Treatment: Ranolazine PR 1000 mg bid (n = 277) | p value |
|---|---|---|---|
| **LAN User** | | | |
| n | 122 | 129 | 0.15 (CMH) |
| Trimmed Mean (SE) | 3.33 (0.31) | 2.91 (0.31) | |
| Median | 2.65 | 2.13 | |
| 25$^{th}$ Percentile – 75$^{th}$ Percentile | 1.52 – 4.43 | 1.33 – 3.96 | |
| Min – Max | 0.00 – 160.26 | 0.00 – 47.33 | |
| Mean (SE) | 5.67 (1.44) | 3.80 (0.49) | |
| **Non-LAN User** | | | |
| n | 159 | 148 | 0.16 (CMH) |
| Trimmed Mean (SE) | 3.17 (0.26) | 2.74 (0.22) | |
| Median | 2.29 | 2.20 | |
| 25$^{th}$ Percentile – 75$^{th}$ Percentile | 1.34 – 3.76 | 1.15 – 3.35 | |
| Min – Max | 0.00 – 17.17 | 0.00 – 17.67 | |
| Mean (SE) | 3.26 (0.26) | 2.84 (0.23) | |

CMH = Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.
LAN = Long-acting nitrate; SE = Standard error.
Trimmed mean in each subgroup is calculated by excluding the data points that were trimmed from the overall analysis.

**Table 9 - Average Weekly Rate of Nitroglycerin Consumption During the 6-Week Double-blind Treatment Phase by Concomitant Use of LANs – Study CVT 3037**

| Average Weekly Rate of Nitroglycerin Consumption (doses/week) | Treatment: Placebo (n = 281) | Treatment: Ranolazine PR 1000 mg bid (n = 277) | p value |
|---|---|---|---|
| **LAN User** | | | |
| n | 122 | 129 | 0.008 (CMH) |
| Trimmed Mean (SE) | 2.96 (0.35) | 2.22 (0.33) | |
| Median | 1.98 | 1.43 | |
| 25th Percentile – 75th Percentile | 0.93 – 4.62 | 0.51 – 3.00 | |
| Min – Max | 0.00 – 111.82 | 0.00 – 62.21 | |
| Mean (SE) | 4.96 (1.19) | 3.67 (0.76) | |
| **Non-LAN User** | | | |
| n | 159 | 148 | 0.24 (CMH) |
| Trimmed Mean (SE) | 2.37 (0.26) | 1.79 (0.21) | |
| Median | 1.30 | 1.18 | |
| 25th Percentile – 75th Percentile | 0.33 – 3.11 | 0.31 – 2.31 | |
| Min – Max | 0.00 – 22.50 | 0.00 – 19.00 | |
| Mean (SE) | 2.50 (0.27) | 1.90 (0.22) | |

CMH = Cochran-Mantel-Haenszel test of equality of mean scores based on modified ridit score, stratified by pooled center.
Trimmed mean in each subgroup is calculated by excluding the data points that were trimmed from the overall analysis.
LAN = Long-acting nitrate; SE = Standard error

Overall, ranolazine 1000 mg b.i.d. did reduce the number of attacks per week (as the primary outcome parameter), and nitroglycerin consumption decreased similarly. The mean reduction was less than one attack per week. It has not been investigated if similar results are achieved if ranolazine is added to optimised doses of a beta-blocker or the combination of a beta-blocker and a calcium antagonist. Therefore, study CVT 3037 has not strictly included a patient population reflected in the SPC, and thus was considered to be merely supportive.

**Study CVT 3036 (MERLIN-TIMI 36)**

A report regarding CVT 3036 was submitted at day 121 during the evaluation. The study was not included in the primary dossier. The studied population had an acute coronary syndrome (ACS) as a prerequisite for inclusion. It was therefore considered to be a somewhat different population than studied previously.

Study design
CVT 3036 was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled clinical trial designed to evaluate the efficacy and safety of ranolazine for long-term treatment in patients with non-ST elevation acute coronary syndromes (ACS) treated with other standard therapy. Patients received either placebo or ranolazine IV. for up to 96 hours, followed by ranolazine 1000 mg bid per for approximately 12 months.

Objectives
The primary efficacy objective was 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.

Safety objectives were to evaluate ranolazine compared to placebo with respect to occurrence of the following endpoints between randomization and the end of follow-up:

- death from any cause
- time to first occurrence of either death from any cause or any cardiovascular hospitalization
- frequency of symptomatic documented arrhythmia
- frequency of clinically significant arrhythmias detected during 7 day continuous ECG monitoring

- serious adverse events (SAEs) related to study drug
- laboratory abnormalities considered clinically significant by physician(s) caring for the patient

Results

A total of 6,560 patients (3,281 placebo, 3,279 ranolazine) were randomized into the study and included in the ITT analysis population; of these, 6,541 (>99%) patients (3,273 placebo, 3,268 ranolazine) received at least one dose of study drug.

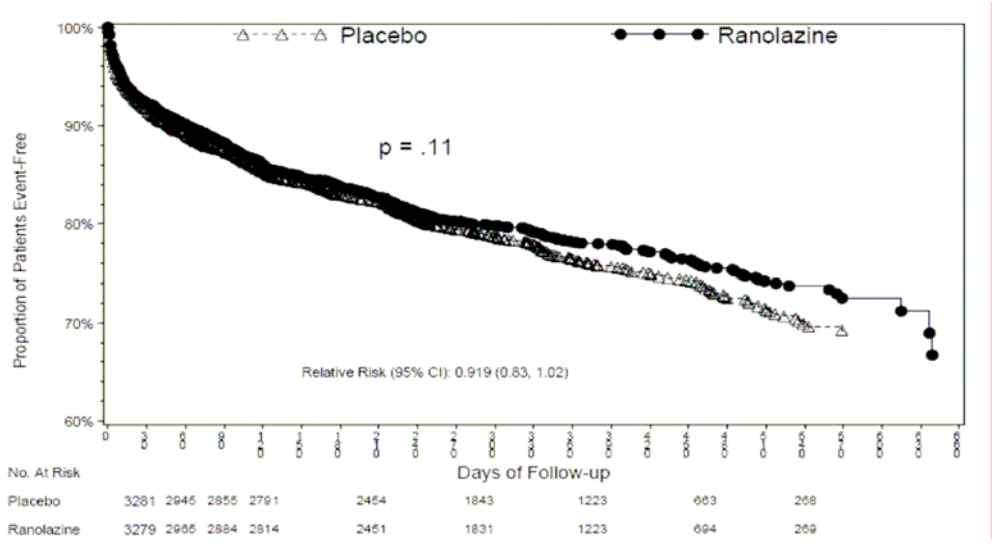
In general, patients received current standard of care prior to enrollment in the study, which continued throughout the treatment period.

Clinical efficacy results in study CVT 3036

Key results are the following:

- Patients treated with ranolazine did not have a significantly reduced risk of occurrence of the primary endpoint (CV death, MI, or recurrent ischemia) compared to patients treated with placebo
- There was no evidence of a benefit of ranolazine treatment with respect to CV death or MI
- However, the risk of recurrent ischemia (defined as worsening angina or ischemia requiring additional therapy and severe recurrent ischemia, showing ECG changes, leading to hospitalization, or prompting revascularization) was reduced by ranolazine
- In addition, worsening angina requiring intensification of antianginal medications was reduced with ranolazine compared to placebo. Concomitant use of antianginal medications was less frequent with long-term ranolazine treatment compared to placebo
- The results indicate that ranolazine was associated with improvement in the angina frequency dimension of the SAQ compared to placebo patients at Month 4. The physical limitation dimension of the SAQ showed no evidence of a reduction at Month 4
- A subgroup analysis of patients with chronic angina at study-entry indicates that ranolazine prolonged duration of exercise during ETT, reduced the need for additional antianginal medications, and improved QOL as measured by the angina frequency, treatment satisfaction and disease perception dimensions of the SAQ

**Figure 2 - Time from Randomization to First Occurrence of CV Death, MI, or Recurrent Ischemia**




Despite the fact that study CVT 3036 failed concerning the primary objective, some support is achieved for an anti-ischemic effect from some of the secondary end points: Additional antianginal medications was needed less often with ranolazine: 175 (5.3%) patients in the placebo group experienced worsening angina or ischemia that required additional therapy during the study, as compared to 134 (4.1%) in the ranolazine group. A quality of live assessment with the Seattle Angina Questionnaire (SAQ) in patients with a history of angina showed a benefit for ranolazine treatment. In patients with a history of angina, the duration of exercise (combining treadmill and bicycle

assessments) was significantly longer in patients treated with ranolazine (513.7±7.2 seconds) vs. placebo (482.7±7.4 seconds), with the effect observed being larger for patients who exercised on the treadmill compared to the bicycle. Taken together, the study therefore showed an effect of ranolazine, although this was considered to be modest.

- Clinical efficacy in special populations (age, race and gender)

No specific studies were performed in diabetics, patients with heart failure or chronic obstructive lung disease, but both in study CVT 3033 and CVT 3031 patients with diabetes (n=235), heart failure (n=274) and chronic obstructive lung disease (n=71) were included. In diabetic patients the exercise duration increased similarly compared to the non-diabetic patients. Heart failure patients showed similar improvements as patients without heart failure in all exercise variables at trough. At peak there was a significantly greater increase in both exercise duration and time to 1 mm ST segment depression among patients with heart failure. For the obstructive lung disease patients the improvement was similar as for those without such disease.

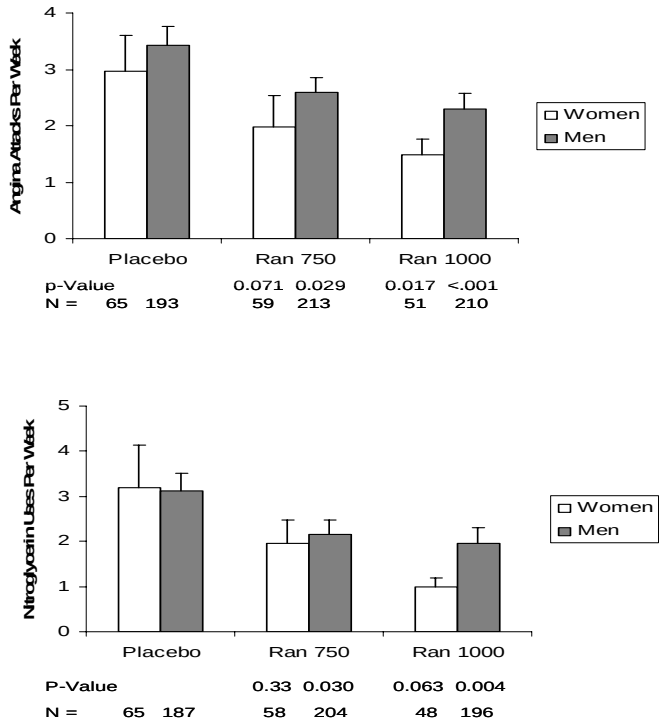
The exercise performance improving effect in females at peak and trough is reduced to 27.5% and to 42.2% of that in males in the dose range of 500 mg to 1500 mg b.i.d. There were significantly smaller improvements in time to onset of angina among females at peak but not at trough.

**Table 10 - Change from Baseline in Exercise Treadmill Test Duration (sec) at Trough at Week 12 Using LOCF. Subgroup Analysis by Gender, study CVT 3033**

| | Ran SR 750 mg vs Placebo | | Ran SR 1000 mg vs Placebo | |
|---|---|---|---|---|
| | Gender | | Gender | |
| Statistic | Female | Male | Female | Male |
| Mean Difference | 1.3 | 28.9 | 6.6 | 26.1 |
| S.E. of Mean Difference | 22.5 | 12.4 | 23.4 | 12.5 |
| 95% Confidence Interval | (-42.9,45.5) | (4.5,53.2) | (-37.4,54.6) | (1.6,50.6) |
| P-value | 0.95 | 0.020 | 0.71 | 0.037 |

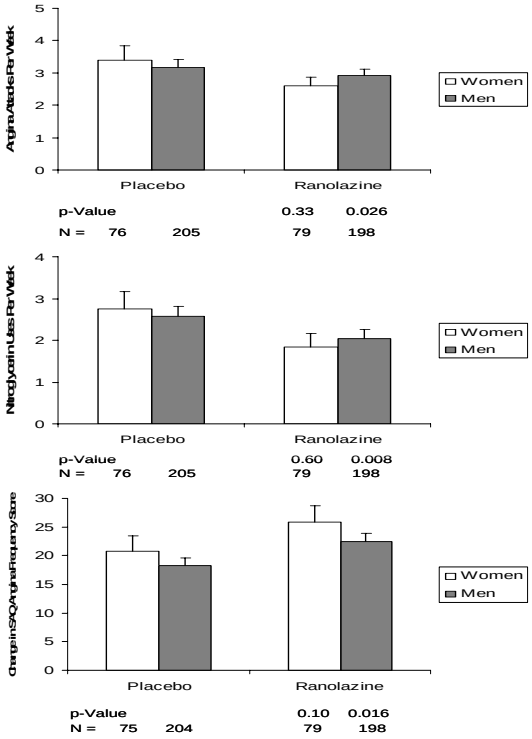
As is seen in table 10, the results in women are not significant and not of any clinical importance. It was noted previously that women showed less improvement compared to men. There is a difference between men and women regarding the results on ETT, but in both CVT 3033 and CVT 3037, there was a decreases in angina frequency and nitroglycerin consumption with ranolazine treatment compared to placebo appeared comparable between women and men (fig 3 and 4, respectively). In addition, in CVT 3037, improvement in the angina frequency dimension of the SAQ with ranolazine treatment was also comparable between women and men (fig 3).

**Figure 3 - Average Weekly Angina Frequency and Nitroglycerin Use Over 12 Weeks in Women and Men (CVT 3033)**




Note: P-value from comparison to placebo using analysis of covariance on ranked data with effects for treatment, background therapy, pooled site, gender and the interaction of treatment with gender.

**Figure 4 - Average Weekly Angina Frequency, Nitroglycerin Use Over 6 Weeks, and Change from Baseline in SAQ Score in Women and Men (CVT 3037)**




Note: P-values from comparison to placebo using Cochran-Mantel-Haenszel test for equality of mean modified ridit score, stratifying by pooled center (angina frequency and NTG use) and analysis of covariance with effects for treatment, pooled site and baseline value (change in SAQ score).

In CVT 3036, 35% of the patients were female, and the results of this study support the conclusion of the earlier studies. An exploratory analysis showed a significant reduction by ranolazine in the risk of recurrent ischemia (relative risk 0.865, 95% CI=0.76, 0.98; p=0.027). There was no evidence that this effect was less in women (relative risk 0.711) than in men (relative risk 0.966, treatment by subgroup interaction test, p=0.026) (Table 11).

**Table 11 - Subgroup Efficacy Analysis: Time from Randomization to First Occurrence of Recurrent Ischemia by Gender**

| | Male | | Female | |
|---|---|---|---|---|
| | Placebo (n=2096) | Ranolazine (n=2173) | Placebo (n=1185) | Ranolazine (n=1106) |
| Number of Patients with Events | 296 | 294 | 198 | 135 |
| Relative Risk (Ranolazine:Placebo) | 0.966 | | 0.711 | |
| 95% Confidence Interval | (0.82, 1.14) | | (0.57, 0.88) | |
| *p-value | 0.68 | | 0.002 | |
| p-value (Treatment Subgroup Interaction) | 0.026 | | | |
| Proportion of patients experiencing an event (KM estimates) | | | | |
| 30 days | 3.6% | 4.4% | 5.3% | 3.0% |
| 60 days | 5.4% | 5.5% | 7.2% | 4.5% |
| 90 days | 6.4% | 6.8% | 8.4% | 5.5% |
| 180 days | 9.9% | 10.1% | 12.8% | 9.0% |
| 270 days | 12.7% | 12.4% | 15.5% | 11.6% |
| 360 days | 15.0% | 14.3% | 18.2% | 13.0% |
| 450 days | 16.3% | 15.8% | 20.2% | 14.3% |

| | | | | |
|---|---|---|---|---|
| 540 days | 19.2% | 17.7% | 21.4% | 16.6% |

Note: *p-value from log-rank test stratifying by the intention for early invasive management. Relative risk estimates from Cox regression model stratifying by the intention for early invasive management. KM=Kaplan Meier.

It is concluded that the additional data mainly from study CVT 3036 is reassuring. There is an effect also in women, although it is more difficult to show this with a standard ETT.

**Clinical safety**

The data on long term safety, that were provided by the applicant initially, were considered to be insufficient by the CHMP. The applicant then provided additional safety data, in particular from study CVT 3036, as summarized subsequently.

- Patient exposure

The ISD (CVT 3036 not included) includes data from 3,463 subjects/patients who received ranolazine (any formulation) and 1,829 subject/patients who received placebo. Exposure to ranolazine ranged from a single dose to >8 years over a dose range of 10 mg once daily to 2250 mg *b.i.d.* The total exposure to ranolazine in the ISD is 3,669 patient-years.
Data from study CVT 3036 is listed in a subsequent section.

- Adverse events

Adverse events were collected by routine monitoring and reporting. In table 12 below the incidence of adverse events in subjects/patients on study medication at doses up to 1,000 mg bid from the ISD and Phase 2/3 controlled angina studies are shown.

**Table 12**

| System Organ Class<br>Preferred Term | Number (%) of Subjects/Patients | | | |
|---|---|---|---|---|
| | Integrated Safety Database | | Phase 2/3 PR Controlled Angina Studies | |
| | Total Ranolazine (n = 3,463) | Total Placebo (n = 1,829) | Total Ranolazine (n = 1,030) | Placebo (n = 738) |
| **Mean Duration of Exposure (days)** | 387 | 28 | 61 | 52 |
| **Total Patients with Any AEs** | 2,087 (60.3) | 532 (29.1) | 394 (38.3) | 204 (27.6) |
| **Blood and Lymphatic System Disorders** | | | | |
| Anaemia | 49 (1.4) | 2 (0.1) | 1 (< 0.1) | 2 (0.3) |
| **Cardiac Disorders** | | | | |
| Acute myocardial infarction | 46 (1.3) | 2 (0.1) | 3 (0.3) | 2 (0.3) |
| Angina pectoris | 196 (5.7) | 18 (1.0) | 25 (2.4) | 13 (1.8) |
| Angina unstable | 85 (2.5) | 10 (0.5) | 7 (0.7) | 6 (0.8) |
| Cardiac failure congestive | 35 (1.0) | 3 (0.2) | 5 (0.5) | 3 (0.4) |
| Myocardial infarction | 57 (1.6) | 1 (0.1) | 4 (0.4) | 0 |
| Palpitations | 74 (2.1) | 17 (0.9) | 9 (0.9) | 7 (0.9) |
| **Ear and Labyrinth Disorders** | | | | |
| Vertigo | 50 (1.4) | 5 (0.3) | 12 (1.2) | 4 (0.5) |
| **Gastrointestinal Disorders** | | | | |
| Abdominal pain | 45 (1.3) | 5 (0.3) | 9 (0.9) | 1 (0.1) |
| Abdominal pain upper | 76 (2.2) | 12 (0.7) | 10 (1.0) | 2 (0.3) |
| Constipation | 245 (7.1) | 10 (0.5) | 74 (7.2) | 9 (1.2) |
| Diarrhoea | 86 (2.5) | 20 (1.1) | 7 (0.7) | 8 (1.1) |
| Dyspepsia | 129 (3.7) | 20 (1.1) | 13 (1.3) | 4 (0.5) |

| System Organ Class<br>Preferred Term | Number (%) of Subjects/Patients | | | |
|---|---|---|---|---|
| | Integrated Safety Database | | Phase 2/3 PR Controlled Angina Studies | |
| | Total Ranolazine<br>(n = 3,463) | Total Placebo<br>(n = 1,829) | Total Ranolazine<br>(n = 1,030) | Placebo<br>(n = 738) |
| Nausea | 266 (7.7) | 20 (1.1) | 53 (5.1) | 6 (0.8) |
| Vomiting | 61 (1.8) | 9 (0.5) | 11 (1.1) | 1 (0.1) |
| **General Disorders and Administration Site Conditions** | | | | |
| Asthenia | 122 (3.5) | 11 (0.6) | 27 (2.6) | 3 (0.4) |
| Chest discomfort | 33 (1.0) | 4 (0.2) | 1 (< 0.1) | 1 (0.1) |
| Chest pain | 121 (3.5) | 17 (0.9) | 7 (0.7) | 6 (0.8) |
| Fatigue | 242 (7.0) | 47 (2.6) | 17 (1.7) | 11 (1.5) |
| Oedema peripheral | 125 (3.6) | 16 (0.9) | 21 (2.0) | 11 (1.5) |
| **Infections and Infestations** | | | | |
| Bronchitis | 48 (1.4) | 2 (0.1) | 4 (0.4) | 1 (0.1) |
| Influenza | 72 (2.1) | 14 (0.8) | 7 (0.7) | 6 (0.8) |
| Nasopharyngitis | 100 (2.9) | 23 (1.3) | 9 (0.9) | 12 (1.6) |
| Pneumonia | 36 (1.0) | 1 (0.1) | 4 (0.4) | 1 (0.1) |
| Upper respiratory tract infection | 61 (1.8) | 12 (0.7) | 5 (0.5) | 4 (0.5) |
| Urinary tract infection | 46 (1.3) | 4 (0.2) | 2 (0.2) | 0 |
| **Investigations** | | | | |
| Blood glucose increased | 35 (1.0) | 11 (0.6) | 8 (0.8) | 7 (0.9) |
| **Metabolism and Nutrition Disorders** | | | | |
| Diabetes mellitus | 41 (1.2) | 1 (0.1) | 6 (0.6) | 1 (0.1.) |

| System Organ Class<br>Preferred Term | Number (%) of Subjects/Patients | | | |
|---|---|---|---|---|
| | Integrated Safety Database | | Phase 2/3 PR Controlled Angina Studies | |
| | Total Ranolazine<br>(n = 3,463) | Total Placebo<br>(n = 1,829) | Total Ranolazine<br>(n = 1,030) | Placebo<br>(n = 738) |
| **Vascular Disorders** | | | | |
| Hypertension | 81 (2.3) | 5 (0.3) | 5 (0.5) | 4 (0.5) |
| Hypotension | 51 (1.5) | 4 (0.2) | 7 (0.7) | 4 (0.5) |
| Orthostatic hypotension | 40 (1.2) | 0 | 1 (< 0.1) | 0 |

Discontinuations due to AEs occurred infrequently, indicating that ranolazine was generally well tolerated at oral doses within the therapeutic range. In the ISD, AEs leading to discontinuation occurred in 8.9% of Ranolazine-treated patients.

The most commonly reported AEs leading to discontinuation for all ranolazine-treated subjects/patients in both the ISD and the Phase 2/3 PR controlled angina studies subset populations, respectively, were dizziness, nausea, and angina pectoris.

**Table 13 - Incidence of Most Common Treatment-emergent AEs Resulting in Discontinuation Reported for ≥0.5% of Subjects/Patients - Integrated Safety Database and Phase 2/3 PR Controlled Angina Studies**

| Category | Number (%) of Subjects/Patients | | | |
|---|---|---|---|---|
| | Integrated Safety Database | | Phase 2/3 PR Controlled Angina Studies | |
| | Total Ranolazine (n = 3,463) | Total Placebo (n = 1,829) | Total Ranolazine (n = 1,030) | Placebo (n = 738) |
| **Mean Duration of Exposure (days)** | 387 | 28 | 61 | 52 |
| **Total Subjects/Patients who Discontinued Due to AEs** | 309 (8.9) | 35 (1.9) | 65 (6.3) | 22 (3.0) |
| **Cardiac Disorders** | | | | |
| Acute myocardial infarction | 16 (0.5) | 1 (<0.1) | 2 (0.2) | 1 (0.1) |
| Angina pectoris | 23 (0.7) | 3 (0.2) | 4 (0.4) | 1 (0.1) |
| Angina unstable | 20 (0.6) | 8 (0.4) | 5 (0.7) | 5 (0.5) |
| **Digestive system** | | | | |
| Nausea | 33 (1.0) | 1 (< 0.1) | 11 (1.1) | 0 |
| Constipation | 15 (0.4) | 0 | 6 (0.6) | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Asthenia | 12 (0.3) | 0 | 5 (0.5) | 0 |
| **Nervous system** | | | | |
| Dizziness | 33 (1.0) | 1 (< 0.1) | 13 (1.3) | 1 (0.1) |
| Headache | 17 (0.5) | 1 (< 0.1) | 5 (0.5) | 0 |

- Adverse Events at High Doses

An evaluation of the safety experience with ranolazine PR doses above the initially proposed maximum recommended therapeutic dose of 1000 mg bid is based on data from Studies CVT 3031 and CVT 3023. In addition, CVT 3111 provides safety information in healthy subjects using supratherapeutic IV dosing. The data from CVT 3031 showed that increasing the dose of ranolazine from 1000 mg bid to 1500 mg bid resulted in a disproportionate increase in the most frequent AEs, including asthenia (9.8 times as high), nausea (7.8 times as high), vomiting (3.5 times as high), dizziness (2.7 times as high), headache (2.5 times as high), and constipation (2 times as high). Data from the tolerability studies 3111 and 3023 are discussed below.

- Serious adverse events

**Table 14 - Incidence of Treatment-emergent SAEs Reported for ≥0.5% of Subjects/Patients - Integrated Safety Database and Phase 2/3 PR Controlled Angina Studies**

| Body System Preferred Term | Number (%) of Subjects/Patients | | | |
|---|---|---|---|---|
| | Integrated Safety Database | | Phase 2/3 PR Controlled Angina Studies | |
| | Total Ranolazine (n = 3,463) | Total Placebo (n = 1,829) | Total Ranolazine (n = 1,030) | Total Placebo (n = 738) |
| **Mean Duration of Exposure (days)** | 387 | 28 | 61 | 52 |
| **Total Subjects/Patients with Any SAEs** | 518 (15.0) | 36 (2.0) | 56 (5.4) | 22 (3.0) |
| **Cardiac Disorders** | | | | |
| Acute coronary syndrome | 16 (0.5) | 0 | 0 | 0 |
| Acute myocardial infarction | 46 (1.3) | 2 (0.1) | 1 (< 0.1) | 0 |
| Angina pectoris | 59 (1.7) | 6 (0.3) | 5 (0.5) | 3 (0.4) |
| Angina unstable | 80 (2.3) | 10 (0.5) | 6 (0.6) | 6 (0.8) |
| Cardiac failure congestive | 16 (0.5) | 0 | 0 | 0 |
| Myocardial infarction | 56 (1.6) | 1 (< 0.1) | 4 (0.4) | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Chest pain | 32 (0.9) | 1 (< 0.1) | 2 (0.2) | 1 (0.1) |
| **Infections and Infestations** | | | | |
| Pneumonia | 17 (0.5) | 1 (< 0.1) | 3 (0.3) | 1 (0.1) |
| **Nervous System Disorders** | | | | |
| Syncope | 16 (0.5) | 0 | 4 (0.4) | 0 |
| Transient ischaemic attack | 16 (0.5) | 1 (< 0.1) | 1 (< 0.1) | 0 |

The most frequently reported SAEs were unstable angina and angina pectoris, occurring at similar frequencies with ranolazine, which is not unexpected in this patient population studied. Among the less frequent but medically important SAEs was syncope. Review of available information on all syncope cases in patients treated with ranolazine in the ISD revealed that most of these cases could be attributed to vasovagal or orthostatic aetiology. There was no evidence of association with ventricular arrhythmias, even in studies in which ranolazine concentrations far exceeded therapeutic levels. Other SAEs mirrored the general profile of AEs. The incidence of SAEs during the long-term studies was 87/143 (60.8%) in Study CVT 3032 and 289/1,108 (26.1%) in Study CVT 3034. The most common SAEs in both long-term studies were angina pectoris, MI, and unstable angina. Syncope was reported as an SAE for nine patients and vasovagal syncope for an additional two patients, of 1,251 in the long term, follow-up studies.

- Deaths

Deaths in the studies were predominantly due to cardiovascular events. As of August 2006, a total of 110 (2.7%; 110/4,027) patient deaths were identified in all 87 ranolazine clinical studies. Twelve of the 110 deaths occurred during the controlled observation period from the Phase 2/3 IR and PR controlled angina studies (n = 2,667), and one patient died in one of the 16 early studies not included in the ISD. Ninety-seven of 110 patients died during the open-label, long-term, follow-up studies; 71 patients died during treatment (including those who died one day after taking their last dose of ranolazine), and 26 patients died after discontinuation. Because these studies did not include a placebo comparison group, no conclusions regarding mortality can be drawn directly from these data. Not unexpectedly, 88/110 deaths were due to cardiovascular causes, including 38 deaths due to MI. Among cardiovascular deaths 22/88 (25%) deaths were reported as or attributed to sudden death, and 7/88 (8%) were reported as ventricular fibrillation/tachycardia (VT/VF) or cardiac arrest. Twenty-two patients died from non-cardiovascular causes including cancer, trauma, respiratory failure, and sepsis; there were three deaths of unknown cause.

- Laboratory findings

No clinically meaningful changes were observed in electrolytes, liver function, endocrine function, or urinalysis parameters. Small mean changes were observed in haematological parameters (haemoglobin, haematocrit, eosinophils, and lymphocytes). Ranolazine produced small mean increases in blood urea nitrogen (BUN) and creatinine, which generally remained stable over time, and were reversible with discontinuation of ranolazine.

- Electrocardiography, including results from study CVT 3036

The effects of ranolazine on ECG parameters have been well characterized in healthy volunteers and chronic angina patients at mean ranolazine plasma concentrations covering the proposed clinical dosing regimen. The results of these analyses show that treatment with ranolazine was associated with dose-related increases in PR and QRS interval, and there were small mean increases in QTc from baseline.

The mean increase in QTc from baseline in the Phase 2/3 PR controlled angina studies was small: QTcB = 2.1–4.6 msec, and QTcF = 1.9–5.4 msec (from CVT 3031 and CVT 3033 only) through the maximum recommended dose of 1000 mg bid. This increase in QTc did not become more pronounced over time during long-term open-label treatment. Outliers of QTc measurements (defined as QTc increase from baseline >60 msec or >500 msec) were observed to occur sporadically, but more often in the ranolazine treated groups. Female patients did not appear to be at greater risk for developing an outlier QTc value compared with male patients.

A population-based analysis of combined data using data from 16 clinical studies of 1,308 patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/mL, which is approximately equal to 2 to 7 msec *increase* over the plasma concentration range for ranolazine 500 to 1000 mg bid. Age, weight, gender, race, diabetes, presence or absence of heart failure, baseline heart rate, baseline QTc, dose (single and total daily dose), patient status (healthy volunteer/patient), ranolazine formulation, and study did not affect the slope of the relationship in the population PK model.
A prolongation of QT was observed in patients with both mild and moderate hepatic impairment in study CVT 3018 (pharmacokinetic study in patients with hepatic impairment).

Analysis of ECG data in the population of patients participating in CVT 3031 and CVT 3033, and continuing treatment in the long-term extension studies CVT 3032 and CVT 3034 (mean duration of exposure in this analysis was 1,080 days) showed that, in general, the incidence of QTc outlier values (defined as either an increase in QTc from baseline >60 msec or a value >500 msec) was rare and sporadic. Outlier values were more common on ranolazine than on placebo, and their incidence (independent of the definition applied) was dose-dependent, with the highest incidence of outliers associated with the 1500 mg bid dose. Of patients treated with ranolazine 1000 mg bid, 4.3% had QTcF outlier values. There have been no reported cases of TdP in any clinical study of ranolazine in 3,669 patient-years of treatment.

The QT-effects of ranolazine appeared to be well characterised and are dose-dependent. So far there has been no reported case of TdP during 3, 669 patient-years exposure to the drug. Since such an arrhythmia is a rare occasion, this is not particularly surprising. However, the data submitted indicates that ranolazine's arrhythmic potential is relatively low, but with very high plasma concentrations, this was considered to become problematic. The safety results from study CVT 3036 have, however, reduced the concerns for an arrhythmogenic effect of ranolazine, as presented in the subsequent section.

- Discontinuation due to AES

Discontinuations due to AEs occurred infrequently, indicating that ranolazine was generally well tolerated at oral doses within the therapeutic range. In the Phase 2/3 PR controlled angina studies the incidence of AEs leading to study discontinuation was 6.3% for ranolazine-treated patients compared with 3.0% for placebo-treated patients (table 17). In the ISD, AEs leading to discontinuation occurred in 8.9% of ranolazine-treated patients.

The most commonly reported AEs leading to discontinuation for all ranolazine-treated subjects/patients were dizziness, nausea, and angina pectoris. In the Phase 2/3 PR controlled angina studies population, the frequency of discontinuation due to angina (including unstable angina) was approximately the same for both ranolazine and placebo. In the ISD, only two treatment-emergent AEs (dizziness and nausea) occurred with a frequency of at least 1% in either ranolazine- or placebo-treated subjects/patients and resulted in discontinuation. The majority of treatment-emergent AEs leading to discontinuation occurred at a low frequency (usually single occurrences). The types of AEs leading to discontinuation were the same as those observed overall.

**STUDY CVT 3036**

Safety results

This study with its large number of participant contributes substantially to the safety data base. It is also the study with the longest duration. In general no new safety issues emerged from CVT 3036, which was considered to be reassuring.

**Table 15 - Treatment-emergent Adverse Events with a Frequency of > 3%**

| System Organ Class<br>Preferred Term | Placebo<br>(n=3273) | Ranolazine<br>(n=3268) |
|---|---|---|
| All | 2403 ( 73%) | 2474 ( 76%) |
| Blood and lymphatic system disorders | 119 ( 4%) | 140 ( 4%) |
| Cardiac disorders | 1107 ( 34%) | 1062 ( 32%) |
| Angina unstable | 372 ( 11%) | 332 ( 10%) |
| Angina pectoris | 256 ( 8%) | 256 ( 8%) |
| Cardiac failure | 173 ( 5%) | 156 ( 5%) |
| Myocardial infarction | 140 ( 4%) | 127 ( 4%) |
| Atrial fibrillation | 135 ( 4%) | 96 ( 3%) |
| Gastrointestinal disorders | 675 ( 21%) | 902 ( 28%) |
| Nausea | 196 ( 6%) | 302 ( 9%) |
| Constipation | 114 ( 3%) | 297 ( 9%) |
| Vomiting | 86 ( 3%) | 129 ( 4%) |
| General disorders and administration site conditions | 839 ( 26%) | 842 ( 26%) |
| Chest pain | 433 ( 13%) | 356 ( 11%) |
| Asthenia | 88 ( 3%) | 158 ( 5%) |
| Fatigue | 89 ( 3%) | 139 ( 4%) |
| Infections and infestations | 479 ( 15%) | 449 ( 14%) |
| Injury, poisoning and procedural complications | 220 ( 7%) | 263 ( 8%) |
| Investigations | 305 ( 9%) | 339 ( 10%) |
| Metabolism and nutrition disorders | 310 ( 9%) | 318 ( 10%) |
| Musculoskeletal and connective tissue disorders | 445 ( 14%) | 412 ( 13%) |
| Nervous system disorders | 694 ( 21%) | 790 ( 24%) |
| Dizziness | 224 ( 7%) | 411 ( 13%) |
| Headache | 295 ( 9%) | 238 ( 7%) |
| Syncope* | 55 ( 2%) | 68 ( 2%) |
| Syncope vasovagal* | 18 ( <1%) | 38 ( 1%) |
| Loss of consciousness* | 5 ( <1%) | 7 ( <1%) |
| Psychiatric disorders | 213 ( 7%) | 269 ( 8%) |
| Renal and urinary disorders | 155 ( 5%) | 220 ( 7%) |
| Respiratory, thoracic and mediastinal disorders | 429 ( 13%) | 476 ( 15%) |
| Cough | 90 ( 3%) | 130 ( 4%) |
| Dyspnoea | 126 ( 4%) | 126 ( 4%) |
| Skin and subcutaneous tissue disorders | 191 ( 6%) | 215 ( 7%) |
| Vascular disorders | 441 ( 13%) | 490 ( 15%) |
| Hypotension | 104 ( 3%) | 160 ( 5%) |
| Hypertension | 141 ( 4%) | 113 ( 3%) |

*although < 3% frequency, included in this table for special interest

Serious Adverse Events

The number of patients experiencing SAEs during the study (both IV and oral dosing periods) was similar in the placebo (1,122/3,273 [34%]) and ranolazine (1,126/3,268 [34%]) treatment groups. Cardiovascular disorders (22% in both groups) were the most frequently reported SAEs and included unstable angina, angina pectoris, cardiac failure, MI, and acute MI.

**Table 16 - Summary of Severe Treatment-emergent Adverse Events with a Frequency of ≥ 1%**

| System Organ Class<br>Preferred Term | Placebo<br>(n=3273) | Ranolazine<br>(n=3268) |
|---|---|---|
| All | 545 ( 17%) | 579 ( 18%) |
| Cardiac disorders | 300 ( 9%) | 295 ( 9%) |
| Cardiac failure | 86 ( 3%) | 76 ( 2%) |
| Myocardial infarction | 76 ( 2%) | 62 ( 2%) |
| Angina unstable | 72 ( 2%) | 61 ( 2%) |
| Acute myocardial infarction | 54 ( 2%) | 50 ( 2%) |
| Gastrointestinal disorders | 47 ( 1%) | 53 ( 2%) |
| General disorders and administration site conditions | 82 ( 3%) | 74 ( 2%) |
| Sudden death | 36 ( 1%) | 28 ( <1%) |
| Infections and infestations | 46 ( 1%) | 40 ( 1%) |
| Injury, poisoning and procedural complications | 35 ( 1%) | 41 ( 1%) |
| Nervous system disorders | 62 ( 2%) | 72 ( 2%) |
| Respiratory, thoracic & mediastinal disorders | 35 ( 1%) | 43 ( 1%) |
| Vascular disorders | 35 ( 1%) | 44 ( 1%) |

One concern has been the risk for ranolazine treated patients to develop severe ventricular arrhythmias. The table below shows the results regarding such events in the CVT 3036 study.

**Table 17 - Incidence and Frequency of Symptomatic Documented Arrhythmias**

| | Placebo (n=3273) | Ranolazine (n=3268) | P-value |
|---|---|---|---|
| Incidence of Symptomatic Documented Arrhythmias | 102 ( 3.1%) | 99 ( 3.0%) | .84 (CMH) |
| Incidence of Symptomatic Documented Arrhythmia by Category | | | |
| Ventricular arrhythmia | 29 ( 0.9%) | 22 ( 0.7%) | |
| Supraventricular arrhythmia | 41 ( 1.3%) | 38 ( 1.2%) | |
| Bradyarrhythmia | 29 ( 0.9%) | 34 ( 1.0%) | |
| Cardiac arrest NOS | 9 ( 0.3%) | 10 ( 0.3%) | |
| Frequency of Symptomatic Documented Arrhythmias per Patient by Category | | | |
| Ventricular arrhythmia | | | |
| 1 | 29 | 20 | |
| 2 | 0 | 1 | |
| 5 | 0 | 1 | |
| Supraventricular arrhythmia | | | |
| 1 | 39 | 34 | |
| 2 | 1 | 4 | |
| 3 | 1 | 0 | |
| Bradyarrhythmia | | | |
| 1 | 29 | 32 | |
| 2 | 0 | 2 | |
| Cardiac arrest NOS | | | |
| 1 | 9 | 10 | |

Note: P-value from Cochran-Mantel-Haenszel general association (CMH) test stratifying by the intention for early invasive management.

The AEs occurring in ranolazine treated patients in CVT 3036 were in general similar to the AEs in other studies. The safety results regarding severe arrhythmias are in particular reassuring.

- Safety in special populations

*Renal Impairment*
Study CVT 3016 was conducted to assess the pharmacokinetics of ranolazine PR in patients with renal impairment, but duration of treatment was only 3 days and steady state had not been reached, which limits the possibilities to draw any conclusions regarding safety in subjects with renal impairment. Additional safety data were obtained in study CVT 3036. This study excluded only patients with end-stage renal failure requiring dialysis, but allowed for enrollment of other patients with severe or moderate renal impairment. Overall, 102 patients with baseline creatinine clearance <30 mL/min (severe renal impairment, 50 placebo and 52 ranolazine) and 1295 patients with baseline creatinine clearance <60 mL/min (moderate renal impairment, 651 placebo and 644 ranolazine) were enrolled in the study. The protocol specified that patients with creatinine clearance <30 mL/min should be treated with a lower dose of ranolazine (40 mg/h, rather than 80 mg/h, IV infusion transitioning to an oral dose of 500 mg bid, rather than 1000 mg bid). Down titration due to renal failure during the study was also allowed. Many of the concentration related adverse events were clearly increased with decreased renal function. All gastrointestinal AEs increased with decreased renal function, and especially the frequency of nausea was clearly related to renal function and was 8, 13 and 23% in patients with CLcr >60, 30-60 and <30 ml/min, respectively. This increase in adverse events in severe renal impairment was obtained although these patients received only 500 mg bid (i.e. a dose reduction of 50%).

*Hepatic Impairment*
Study CVT 3018 considered the effects of ranolazine PR on ranolazine pharmacokinetics in patients with mild and moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Duration of treatment was 3 days. There were no SAEs and no patient discontinued the study early due to an AE. The incidence of all AEs was the same in patients with mild or moderate hepatic disease (50%, 4/8 patients in each group) but higher than that in healthy volunteers (18.8%, 3/16 volunteers). The incidence of treatment-emergent AEs was related to disease severity. As discussed above QT prolongation was more pronounced in these patients. Study 3036 excluded patients with clinically significant hepatic impairment. Hence, safety data in patients with moderate to severe hepatic impairment are lacking from this study.

*Reactive Airway Disease, Heart Failure, Diabetes, Low Blood Pressure and/or Low Heart Rate and/or Prolonged AV Conduction*
The presence of pre-existing reactive airway disease, CHF, diabetes, or low blood pressure and/or low heart rate and/or prolonged AV conduction did not alter the general nature or frequency of treatment-emergent AEs, SAEs, or AEs leading to discontinuation, vital signs, or ECG parameters.

*Age, Gender, and Race*
The treatment-emergent response to ranolazine was similar in all demographic subgroups for all parameters examined and was also similar to the overall Phase 2/3 PR population, with the exception of a higher incidence of ranolazine treatment-emergent AEs in patients ≥75 years of age compared with younger patients. The most frequent AEs observed in patients treated with ranolazine who were ≥75 years of age were constipation (21/114; 18.4%), dizziness (18/114; 15.8%), nausea (13/114; 11.4%), asthenia (9/114; 7.9%), and headache (7/114; 6.1%). Subgroup analyses by race were performed, but the small number of non-Caucasian patients limits the utility of these analyses.

In CVT 3036 AEs and treatment discontinuations due to AEs were more frequent among elderly patients, although SAEs did not show an increased incidence in the ranolazine group compared to placebo. Compared to placebo-treated patients ≥75 years old, those treated with ranolazine had a higher rate of down-titration of study drug (16% vs 9%), mostly due to AEs deemed to be treatment related. Thus, elderly patients apparently were more sensitive to ranolazine than younger patients judging from the occurrence of AEs, especially gastro-intestinal AEs, but also syncope and hypotension was more common. The latter events are particularly worrying since they could lead to other complications such as fractures and other kind of trauma. Consequently, recommendations and warnings are given in sections 4.2, 4.4 and 4.8 of the SPC.

In the earlier studies only 23% of the included patients were women, however, there were no signs of a different safety profile in women. This was also the case in study CVT 3036 (MERLIN-TIMI 36), which included 34% women.

The safety results in the investigated subgroups are not in general different from the overall safety profile. However, the very few non-Caucasians and the few heart failure patients makes the safety profile more uncertain for these groups.

- Studies especially addressing safety and tolerability

*Study 3111*
Study CVT 3111, primarily conducted to assess the effects of ranolazine on the QTc interval, provided information on AEs at high plasma concentrations following IV administration of ranolazine in healthy subjects. There was an increased incidence of AEs including nausea, dizziness/postural dizziness, and headache with increased dose. The following AEs were observed only at the highest target concentrations: blurred vision, diplopia, vasovagal syncope, somnolence, and lethargy. It was not possible to achieve the highest targeted plasma concentration of 15,000 ng/mL in all subjects because of the emergence of intolerable AEs in the seven subjects who actually received this regimen. The average plasma concentration in the two highest dose groups were 8027 ng/ml in the 10,000 ng/ml group and 9196 ng/ml in the 15,000 ng/ml group No cardiac arrhythmias were observed, including the time period during which continuous ECG monitoring was performed.

**Table 18 - Study CVT 3111 Selected Dose-related Adverse Events by Target Ranolazine iv Concentration**

| Adverse Event | Target Ranolazine Concentration (ng/mL) | | | |
|---|---|---|---|---|
| | 2,000 (n = 31) | 4,000 (n = 22) | 10,000 (n = 22) | 15,000 (n = 7) |
| Mean (SD) Obtained plasma concentration | 1813 (353) | 4606 (958) | 8027 (2696) | 9196 (1046) |
| Nausea | 2 (6.5%) | 6 (27.3%) | 10 (45.5%) | 2 (28.6%) |
| Dizziness | 2 (6.5%) | 9 (40.9%) | 14 (63.6%) | 6 (85.7%) |
| Headache | 1 (3.2%) | 7 (31.8%) | 12 (54.5%) | 4 (57.1%) |
| Postural Dizziness | 4 (12.9%) | 3 (13.6%) | 5 (22.7%) | 2 (28.6%) |
| Vision Blurred | 0 | 0 | 5 (22.7%) | 3 (42.9%) |
| Diplopia | 0 | 0 | 2 (9.1%) | 2 (28.6%) |
| Syncope Vasovagal | 0 | 0 | 1 (4.5%) | 2 (28.6%) |
| Syncope | 1 (3.2%) | 0 | 1 (4.5%) | 0 |
| Somnolence | 0 | 0 | 1 (4.5%) | 1 (14.3%) |
| Lethargy | 0 | 0 | 1 (4.5%) | 1 (14.3%) |

Thirteen subjects were withdrawn from this study due to AEs; of these, 10 subjects were prematurely discontinued while receiving ranolazine infusion (4 during the 10,000 ng/mL target treatment ranolazine infusion, and 6 during the 15,000 ng/mL target treatment ranolazine infusion). The ranolazine plasma concentration at the time of discontinuation of the infusion for subjects withdrawn prematurely ranged from 5,340 ng/mL to 10,700 ng/mL.

*CVT 3023*

The primary objective of CVT 3023 was to determine the tolerability of ranolazine ER at oral doses up to 2,250 mg twice a day. The secondary objective was to characterize the adverse events and the changes in vital signs and laboratory parameters associated with these doses. The study was double-blind, randomized, parallel-group with dose escalation. Patients were randomized 1:1:1 within each study centre to one of three treatment regimens, with each treatment regimen having three treatment periods:

**Table 19 - Study CVT 3023 Treatment Regimens**

| Ranolazine Dose (mg, bid) | | | |
|---|---|---|---|
| **Treatment Regimen** | **Treatment Period 1** | **Treatment Period 2** | **Treatment Period 3** |
| | **Days 1–3** | **Days 4–7** | **Days 8–13** |
| 750/750/750 | 750 | 750 | 750 |
| 750/1500/1500 | 750 | 1500 | 1500 |
| 750/1500/2250 | 750 | 1500 | 2250 |

Patients were resident in a clinical unit for 14 days. Adverse events were routinely assessed. Blood samples were collected for determination of ranolazine plasma concentrations. To be enrolled in this study, patients, in short, must have had at least a 3-month history of chronic angina pectoris triggered by physical effort and relieved by rest and/or sublingual nitroglycerin; a diagnosis of coronary artery disease (documented by angiographic evidence of ≥60% stenosis of one or more major arteries, a history of myocardial infarction, a cardiac imaging scan indicating coronary artery disease); or a minimum of 2 weeks treatment with daily chronic anti-anginal medications prior to admission. Tolerability was measured by the number of patients who (1) experienced syncope, diplopia, somnolence, depressed level/loss of consciousness, confusion/disorientation, symptomatic hypotension, dizziness, nausea, vomiting, or (2) had any severe adverse event, or (3) terminated from the study due to an adverse event. Safety was measured through collection of adverse events, identification of serious adverse events, vital signs, laboratory assessments, and electrocardiogram measurements.

Results

A total of 37 patients were enrolled and dosed (12 in 750/750/750, 13 in 750/1,500/1500, and 12 in 750/1500/2250), 23 patients completed the study, and 14 patients prematurely terminated from the study. Tolerability of the ranolazine regimens decreased as the dose increased. The treatment regimens that included doses of 1500 mg bid and 2250 mg bid appeared to be intolerable; the most frequently observed AEs were nausea, dizziness, and vomiting. As many as 14 patients (of 37) terminated early from the study. Five patients were withdrawn from the study due to one or more adverse events, and 1 patient was withdrawn for QTc interval prolongation.

Four patients voluntarily withdrew consent. Two patients were withdrawn by the sponsor, 1 for not having met the study-entrance criteria and 1 for concomitant use of a prohibited medication, and 2 patients were withdrawn because the study-site required evacuation. Only one patient in the lowest dose group terminated prematurely, whereas seven in the highest dose group terminated prematurely. All patients who discontinued Study CVT 3023 due to AEs were treated with either 1500 mg bid or 2250 mg bid of ranolazine and achieved ranolazine plasma concentrations (within 12 hours of the event) in the range of 3,520 ng/mL–14,000 ng/mL. The patient withdrawn due to QTc prolongation was withdrawn on Day 11 after 8 days administration of 1500 mg bid. At time of withdrawal the plasma concentration was 7,210 ng/ml (7 h after dose). The patient had reported dizziness/light headedness or nausea (usually mild) almost every day during ranolazine administration. However, the reported adverse events did not result in withdrawal of the patient.

The results show that the tolerability decreased as the ranolazine dose increased; the number and percent of patients who experienced one or more of the endpoint events were as follows: 1 (8%) patient in the 750/750/750 regimen, 6 (46%) patients in the 750/1500/1500 regimen, and 9 (75%) patients in the 750/1500/2250 regimen. Patients in the 750/1500/2250 group had the highest incidence of the endpoint adverse events compared to patients in the other two treatment regimens, particularly nausea (50%), dizziness (42%), and vomiting (25%). In addition, 4 (33%) patients in the 750/1500/2250 group terminated from the study due to an adverse event, compared to 1 (8%) patient in the 750/1500/1500 group and no patient in the 750/750/750 group.

In summary, CVT 3031, CVT 3023, and CVT 3111 show that there is an increased frequency (often disproportional) of the most commonly reported AEs with increasing doses above 1000 mg bid. Some uncommon events, such as visual disturbance (vision blurred, diplopia), somnolence, or lethargy, have been observed more frequently at doses of ranolazine ≥1500 mg bid, and particularly at corresponding concentrations for iv dosing. These events were most pronounced when the iv formulation was used to achieve exceptionally high plasma concentrations in CVT 3111. No life-threatening events, such as ventricular arrhythmias, were observed in these studies.

*Overall discussion on tolerability*

Study CVT 3023 confirmed the relation between level of exposure of ranolazine and adverse events. Ranolazine adverse events are clearly concentration related. Withdrawal from treatment occurred at plasma concentrations usually >6,000 ng/ml. In study 3033, the plasma concentration 4 h after dose (at approximately $C_{max}$) was about 3000 ng/ml and the concentration 12 h after dose ($C_{min}$) about 2,400 ng/ml (corresponding data in healthy volunteers were 3,800 ng/ml and 1,900 ng/ml) in patients receiving 1000 mg bid. Hence, plasma concentrations that are not tolerated are only 2-3 fold higher than those at 1000 mg bid. The safety margin is thus low. This was of considerable concern to the CHMP considering the large variability in ranolazine pharmacokinetics and the many factors resulting in increased ranolazine exposure.

It is acknowledged that most of the AEs were relatively benign, the most common being dizziness, nausea and vomiting. However, with increasing exposure, as in CVT 3111, more serious AEs occurred, such as disturbed vision, syncope, lethargy and somnolence. The appearance of uncomfortable and disturbing AEs might occur before there are serious AEs, however in routine clinical practice, those early symptoms, such as nausea, would be needed to be interpreted as a sign of increasing exposure to ranolazine.

To address these concerns, warnings and recommendations were implemented in the SPC. Moreover, the applicant has committed to include the concept of a patient alert card, with information for health care professionals as well as patients, alerting to the possible contraindication, needed dose reductions, or precautions, when taken together with some other medicinal products, and for the patient to speak to their doctor, when they have certain specified conditions.

- Safety related to drug-drug interactions and other interactions

Ranolazine has a complex interaction profile with a large risk for increased exposure during co-administration with CYP3A4 inhibitors, P-gp inhibitors and CYP2D6 inhibitors (see section Pharmacokinetics above).

## 2.5 Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

**Risk Management Plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

| Safety issue | Proposed pharmacovigilance activities | Proposed risk minimisation activities |
|---|---|---|
| Identified Risk: Constipation, nausea, vomiting | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion, if warranted | • SPC language (Sections 4.2, 4.4, 4.5, 4.8, and 4.9).<br>Section 4.2: If a patient experiences treatment related adverse events (e.g., nausea, or vomiting), down-titration of Latixa to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.<br>Section 4.4: Caution should be exercised when prescribing or uptitrating ranolazine to patients in whom an increased exposure is expected.<br>Section 4.5: Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (e.g., nausea) may also increase with increased plasma concentrations.<br>Section 4.8: Constipation, nausea, and vomiting were commonly reported as an undesirable effect during clinical trials. Elderly patients (≥ 75 years of age) experienced constipation, nausea and vomiting more frequently than younger patients (< 75 years of age), placebo corrected frequencies: constipation (8% versus 5%), nausea (6% versus 3%), and vomiting (4% versus 1%).<br>Section 4.9: In an oral high-dose tolerability study in angina patients, the incidence of nausea, and vomiting increased in a dose dependent manner.<br>• Patient Alert Card |
| Identified Risk: | • Routine pharmacovigilance | • SPC language (Sections 4.2, 4.4, 4.5, 4.7, 4.8 |

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| Dizziness and Syncope | • Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | and 4.9).<br>Section 4.2: If a patient experiences treatment related adverse events (e.g., dizziness), down-titration of Latixa to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.<br>Section 4.4: Caution should be exercised when prescribing or uptitrating ranolazine to patients in whom an increased exposure is expected.<br>Section 4.5: Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (e.g., dizziness) may also increase with increased plasma concentrations.<br>Section 4.7: Latixa may cause dizziness and blurred vision (see Section 4.8), which may affect the ability to drive and use machines.<br>Section 4.8: Dizziness was commonly reported as an undesirable effect during clinical trials. In patients with mild or moderate renal impairment (creatinine clearance ≥ 30–80 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: dizziness (7% versus 5%).<br>Section 4.9: In an oral high-dose tolerability study in angina patients, the incidence of dizziness increased in a dose-dependent manner.<br>• Patient Alert Card |
| Identified Risk: Confusion | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Section 4.8).<br>Section 4.8: Confusion was uncommonly reported as an undesirable effect during clinical studies. |
| Identified Risk: Hypotension | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Section 4.8).<br>Section 4.8: Hypotension was uncommonly reported as an undesirable effect during clinical studies. |
| Identified Risk: QT prolongation | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Sections 4.4, 4.5, 4.8, 5.1 and 5.2).<br>Section 4.4: Caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval.<br>Section 4.5: There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.<br>Section 4.8: Prolonged QT corrected interval was uncommonly reported as an undesirable |

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| | | effect during clinical studies.<br>Section 5.1: Dose and plasma concentration-related increases in the QTc interval (about 6 msec at 1000 mg twice daily) have been observed in patients treated with Latixa. A population analysis of combined data from 1,308 patients and healthy volunteers demonstrated a mean increase in QTc from baseline of 2.4 msec per 1000 ng/ml ranolazine plasma concentration. This value is consistent with data from pivotal clinical studies.<br>Section 5.2: QT prolongation was more pronounced in patients with moderate hepatic impairment.<br>• Patient Alert Card |
| Important Missing Information:<br>Male infertility | • Routine pharmacovigilance<br>• PSUR discussion if warranted | • No specific risk minimisation activity planned |
| Important Missing Information:<br>Pregnancy, Lactation and<br>Paediatric | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | SPC language (Sections 4.2, 4.6 and 5.2).<br>Section 4.2: Latixa is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.<br>Section 4.6: Pregnancy: The potential risk for humans is unknown. Latixa should not be used during pregnancy unless clearly necessary. Lactation: It is unknown whether ranolazine is excreted in human breast milk. Latixa should not be used during breast-feeding.<br>Section 5.2: The pharmacokinetic parameters of ranolazine have not been studied in the paediatric population (< 18 years). |
| Important Missing Information:<br>Ethnicity other than Caucasian | • Routine pharmacovigilance (Due to confidentiality laws, ethnicity data will not be solicited, but if ethnicity data is volunteered, these data will be collected and included in the individual case reports and PSURs)<br>• PSUR discussion if warranted | • No risk minimisation activity planned |
| Important Missing Information:<br>Safety information for patients<br>with moderate and severe<br>hepatic impairment | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Sections 4.2, 4.3, 4.4, 5.1 and 5.2).<br>Section 4.2 and 4.3: Careful dose titration is recommended in patients with mild hepatic impairment. Latixa is contraindicated in patients with moderate or severe hepatic impairment.<br>Section 4.4: Caution should be exercised when prescribing or uptitrating ranolazine to patients in whom an increased exposure is expected, including in patients with mild hepatic impairment.<br>Section 5.1: Dose and plasma concentration related electrocardiographic effects have been observed in patients treated with Latixa; the slope is higher in patients with clinically significant hepatic impairment.<br>Section 5.2: The pharmacokinetics of ranolazine have been evaluated in patients with mild or moderate hepatic impairment. There are no data in patients with severe |

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| | | hepatic impairment. Ranolazine AUC was unaffected in patients with mild hepatic impairment but increased 1.8-fold in patients with moderate impairment. QT prolongation was more pronounced in these patients.<br>• Patient Alert Card |
| Important Missing Information:<br>Patients with severe and endstage renal disease requiring dialysis | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Sections 4.2, 4.3, 4.4, 4.8, and 5.2).<br>Section 4.2 and 4.3: Careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30–80 mL/min). Latixa is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min).<br>Section 4.4: Caution should be exercised when prescribing or uptitrating ranolazine to patients in whom an increased exposure is expected including those with mild to moderate renal impairment (creatinine clearance 30-80 mL/min). Renal function decreases with age and it is therefore important to check renal function at regular intervals during treatment with ranolazine.<br>Section 4.8: In general, adverse events occurred more frequently in patients with renal impairment. In patients with mild or moderate renal impairment (creatinine clearance ≥ 30–80 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%).<br>Section 5.2: In a study evaluating the influence of renal function on ranolazine pharmacokinetics, ranolazine AUC was on average 1.7- to 2- fold higher in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function. The influence of dialysis on the pharmacokinetics of ranolazine has not been evaluated.<br>• Monitoring of patients with a medical history of severe and end stage renal disease requiring dialysis collected in the postmarketing safety database, for example, data from routine spontaneous reports, anonymous single patient reports and reports from the literature<br>• Patient Alert Card |
| Important Missing Information:<br>(Drug-drug interactions with Class Ia and Class III antiarrhythmics except amiodarone) | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Sections 4.3 and 4.5).<br>Section 4.3: Concomitant administration of Class Ia or Class III antiarrhythmics other than amiodarone is contraindicated.<br>Section 4.5: There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias<br>• Monitoring of concomitant medication in |

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| | | postmarketing data, for example data from routine spontaneous reports, anonymised single patient reports and reports from the literature<br>• PSUR focus on identified drug-drug interactions<br>• Patient Alert Card |
| Important Missing Information:<br>Antihistamines (eg, terfenadine, astemizole, mizolastine), certain antiarrhythmics (eg, quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (eg, imipramine, doxepin, amitriptyline) | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Section 4.5)<br>Section 4.5: There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.<br>• Monitoring of concomitant medication in postmarketing data, for example data from routine spontaneous reports, anonymised single patient reports and reports from the literature<br>• PSUR focus on identified drug-drug interactions<br>• Patient Alert Card |
| Important Missing Information:<br>Real-world safety information for drug-drug interactions with potent CYP3A inhibitors | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion if warranted | • SPC language (Sections 4.2, 4.3, 4.4, and 4.5).<br>Section 4.2: Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors.<br>Section 4.3: Concomitant administration of potent CYP3A4 inhibitors is contraindicated.<br>Section 4.4: Caution should be exercised when prescribing or uptitrating ranolazine with concomitant administration of moderate CYP3A4 inhibitors.<br>Section 4.5: Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (eg, nausea, dizziness) may also increase with increased plasma concentrations<br>• Monitoring of concomitant medication in postmarketing data for example, for example data from routine spontaneous reports, anonymised single patient reports and reports from the literature<br>• PSUR focus on identifiable drug-drug interactions<br>• Patient Alert Card |
| Important Missing Information:<br>Drug-drug Interactions with CYP2D6 substrates which may need to be down-titrated (tricyclic antidepressants and antipsychotics) | • Routine pharmacovigilance<br>• Drug utilization Study: Ranolazine IMS Disease Analyzer Study CVT 303 IMS.001<br>• PSUR discussion, if warranted | • SPC language (Sections 4.4 and 4.5).<br>Section 4.4: The potential risk for increased exposure leading to adverse events in patients lacking CYP2D6 activity (poor metabolisers, PM).<br>Section 4.5: Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine<br>• Monitoring of concomitant medication in postmarketing data, for example data from routine spontaneous reports, anonymised single patient reports and reports from the literature<br>• PSUR focus on identifiable drug-drug interactions |

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| | | • Patient Alert Card |

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

The Safety Specification made by the applicant in the updated RMP includes constipation, nausea, vomiting, dizziness, syncope, hypotension and QT-prolongation as important identified risks. The Safety Specification has been expanded considerably, including information of risk factors for experiencing ADRs such as age, low weight.

In general, two factors dominate the clinical safety aspects of ranolazine; firstly, the narrow therapeutic margin and, secondly, the complicated pharmacokinetics of ranolazine and interaction with concomitant medications. Regarding the problem of complex interactions, see also discussions in the Pharmacokinetic evaluation.

The Pharmacovigilance Plan has includes routine pharmacovigilance and IMS disease analyser data to be collected and analysed.
This study evaluating prescribing patterns and concomitant medication via the IMS Disease Analyzer, could provide valuable information on post marketing use of ranolazine. The Applicant has provided an acceptable synopsis of this study. The interim data will be submitted periodically in the PSURs and submission of final data will be submitted following accrual of 10,000 patients. This is acceptable considering the already existing post-marketing experience.

As for Risk Minimisation activities, this plan has been revised, in line with the comments on the Safety Specification. The Applicant has submitted a "Patient Alert Card" (PAC), which contains information about the risk of increased exposure under certain circumstances. The patient should carry this card, in order to inform other health care providers than the patient's usual (prescribing) physician.
The card includes the contraindications, potential AEs, and the need for the patient to bring a list of all medications to any visit with health care professionals; it is also urges the patient to read carefully the PIL.
This PAC will provide an additional safety measure for the "real world setting", especially in the context of a complicated interaction potential associated with the use of ranolazine.
Both the SPC and the patient information leaflet (PIL) have been updated with information regarding the PAC.
The Applicant has listed several measures to ensure that each patient should be given the PAC. The measures described are adequate. Both pharmacies and health care providers will also have access to the PAC, as this will further ensure that each patient will be provided with it.

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

### Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

### Non-clinical pharmacology and toxicology

Ranolazine's mechanism of action is thought to be selective inhibition of late inward sodium current ($I_{Na}$) relative to peak $I_{Na}$ resulting in a decrease in intracellular Na+ and $Ca^{2+}$ overload and an attenuation of the deleterious electrical and mechanical consequences of $Ca^{2+}$ overload. In the receptor screening assays, ranolazine and its R- and S-enantiomers were found to have significant binding

activity only to α1-adrenergic receptors, β1-adrenergic receptors, β2-adrenergic receptors, and serotonin 5-HT1A and 5-HT2 receptors, however the contribution of these receptor-mediated actions to the anti-ischemic and antianginal effects of ranolazine remains to be established.

Safety pharmacology studies show that ranolazine is generally devoid of detrimental effects at plasma concentrations within the expected therapeutic range. Where effects were observed in safety pharmacology studies, they were in general agreement with the adverse events observed in clinical trials. In addition, in dogs, no significant haemodynamic interaction of ranolazine with long-acting nitrates and the phosphodiesterase-5 inhibitor, sildenafil, was observed.

From the PK point of view, ranolazine was rapidly absorbed after oral administration in all studied species. Ranolazine or its metabolites were distributed widely, including CNS. The adrenals were found to have high concentrations, finding which was considered of relevance as the adrenals were found to be target organs in several toxicity studies, and tumours were found in the adrenals in the rat carcinogenicity study.
It is unknown whether ranolazine or its metabolites passes the placenta and/or secreted into the breast milk of lactating animals. However, based on the general behaviour of the molecule it seems likely; in view of which a warning has been included in section 4.6. of the SPC.

The repeat dose toxicity programme revealed that ranolazine appeared to be associated with toxicity to the central nervous system (CNS) including convulsions, ataxia, prostration, and death. The pattern was relatively consistent across studies of various types and lengths and the effect was thought to be related to high Cmax with the immediate release formulation used in the animal studies. In order to clarify this point a pilot study using a controlled release formulation was proposed. The pilot study however was not feasible as severe toxicity was seen at about the same AUC as previously. The proposed clinical doses therefore can only be supported by the clinical data.

In a Comet assay performed on liver tissue from rats no signs of DNA damage were seen, the results alleviate the remaining concerns about a possible genotoxic or carcinogenic effect of ranolazine or its metabolites. These results are further supported by the additional reassurance of no detectable levels of the metabolite DMA found in human samples, even though they were detected in rat and mouse samples.

In the reproductive toxicology atrophy of the testes and epididymides, and growth retardation was observed, but no malformations of the foetus were seen at doses that were toxic for the pregnant animals. These findings are reflected in warning against the use of ranolazine during pregnancy.

**Efficacy**

In the pivotal study (CVT 3033) ranolazine was studied as an add-on therapy to base-line drugs, of which the respective doses were chosen based on data regarding angina pectoris treatment in European countries. Ranolazine (750 mg bid,1000 mg bid. or placebo) was studied as add-on treatment to atenolol 50 mg od (n=236), amlodipine 5 mg od (n=175), or diltiazem 180 mg od (n=143). All patients (mean age of 64 years) had had chronic stable angina for at least 3 months. The study population was considered to be sufficiently well representative for a broad European population with stable angina. As for the primary efficacy end point, there was a change from baseline in exercise duration at trough after 12 weeks on study drugs with an increase in exercise duration of about 24-30 s; in addition, the onset of angina pectoris was delayed by about 20 s. Both ranolazine groups (750 and 1000 mg b.i.d.) showed similar effects compared to placebo. The design of the study was considered suboptimal regarding the base-line treatment and therefore the Applicant performed a post hoc subgroup analysis in a non-randomised group of patients on a treatment regime considered to be closer to a maximal treatment. The results in this group were similar to the results in the whole patient population, therefore it is concluded that modest beneficial effects of ranolazine can be expected also in maximally dosed patients.

In a supportive study (CVT 3037), ranolazine was studied over 6 weeks in 565 patients having at least 3 angina attacks per week on 10 mg of amlodipine. Over 40% of the patients were also treated with

long acting nitrates. The primary efficacy variable was change in number of patient recorded angina pectoris attacks per week. Ranolazine 1000 mg b.i.d. did reduce the number of attacks per week (as the primary outcome parameter), and nitroglycerin consumption decreased similarly. The mean reduction was less than one attack per week. It has not been investigated if similar results are achieved if ranolazine is added to optimised doses of a beta-blocker or the combination of a beta-blocker and a calcium antagonist. Therefore, study CVT 3037 has not strictly included a patient population reflected in the SPC, and thus was considered to be supportive.

A study in patients with acute coronary syndrome (CVT 3036) failed to show any differences between placebo and ranolazine treated patients in the primary efficacy variable (CV death, MI and recurrent ischemia). There was a modest significant difference in one secondary end point (mainly worsening angina/need for additional antianginal therapy). This study was considered to be supportive from an efficacy point of view. However, the study was of high relevance for the assessment of the safety of ranolazine (see below).

Overall, although the effects on exercise duration and other signs of ischemia were relatively modest, such modest efficacy is not uncommonly seen in trials in patients with stable angina pectoris. There was concern about the clinical relevance of the effects by the CHMP, but a post hoc analysis of the group of maximally dosed patients in CVT 3033 provided some support for the assumption that an effect could be anticipated even in patients with optimised conventional therapy, thus alleviating those concerns. This conclusion was supported by the results from CVT 3037 with 10 mg amlodipine as baseline treatment and, but to a lesser extent, from the results of CVT 3036 in ACS patients. It was concluded that Latixa could be of value in certain patients, especially those who are intolerant to conventional treatment or those who continue to have symptoms despite maximal doses of the usual anti-anginal drugs.

**Safety**

Ranolazine has a complex pharmacokinetic profile with extensive metabolism to a large number of metabolites whereof one metabolite may contribute significantly to the efficacy. The metabolism is catalyzed by both CYP3A4 and CYP2D6. Ranolazine displays non-linear pharmacokinetics with saturable elimination resulting in more than proportional increase in exposure with increased dose. Ranolazine has a large interaction potential with increased exposure during co-administration of CYP3A4 inhibitors, P-gp inhibitors and CYP2D6 inhibitors. Exposure is also increased in several sub-populations such as patient with CYP2D6 poor metaboliser status (PM), patients with renal impairment or hepatic impairment, patients in the lower weight range and in the elderly. Very large increase in exposure could be expected in patients with several risk factors for increased exposure.
Ranolazine is a moderate to potent inhibitor of P-gp and a mild inhibitor of CYP3A4 and is likely also a mild inhibitor of CYP2D6.

The adverse events seen with the use of ranolazine are dose related and usually of moderate intensity. The most common are dizziness, nausea, vomiting and angina pectoris. The ISD includes data from 3,463 subjects/patients who received ranolazine (any formulation) and 1,829 subject/patients who received placebo. Exposure to ranolazine ranged from a single dose to >8 years over a dose range of 10 mg once daily to 2250 mg b.i.d. The total exposure to ranolazine in the ISD is 3,669 patient-years.
The most commonly reported AEs leading to discontinuation for all ranolazine-treated subjects/patients in both the ISD and the Phase 2/3 PR controlled angina studies subset populations, respectively, were dizziness, nausea, and angina pectoris. Among the less frequent but medically important SAEs was syncope. Most of these cases could be attributed to vasovagal or orthostatic aetiology, without any evidence of association with ventricular arrhythmias. With increasing exposure, not only do the number and proportion of patients experiencing AEs increase but also the severity of the AEs increase. A dose-response study (CVT 3031) showed a disproportionate increase in the most frequent AEs, including asthenia, nausea, vomiting, dizziness, headache, and constipation upon increasing the dose of ranolazine from 1000 mg bid to 1500 mg bid. In tolerability study (CVT 3111), AEs observed at the highest target concentrations were: blurred vision, diplopia, vasovagal syncope, somnolence, and lethargy. The QTc interval increases by a mean of 2.4 msec with every 1,000 ng/ml increase in plasma concentration. Outlier values for QTc-prolongation were more common on

ranolazine than on placebo, and their incidence was dose-dependent. In the study in patients with acute coronary syndrome (CVT 3036), the data of which was provided during the evaluation of the application, the occurrence of severe ventricular arrhythmias in the ranolazine group did not increase compared to placebo-treated patients, which did alleviate the concerns of the CHMP. The study did also show a very similar pattern of AEs as outlined above.

Thus, at targeted therapeutic concentrations of ranolazine, the AEs were relatively benign and the frequency of SAEs was low, but this changes with higher plasma levels, with intolerable adverse events at exposure only 2-3 folds higher than the mean exposure at 1000 mg bid. The safety margin is thus low. This was of considerable concern to the CHMP considering the large variability in ranolazine pharmacokinetics and the many factors resulting in increased ranolazine exposure. Given the similar efficacy at 750 mg bid and 1000 mg bid and the dose dependent adverse events, the benefit risk of the 1000 mg bid dose was questioned in the day 180 List of Outstanding Issues. In response to this major objection, the applicant has withdrawn the 1000 mg dose and now ranolazine 750 mg bid is recommended as the maximum dose.

Safety evaluation of different sub-groups with risk for increased exposure in study 3036 reveal an increased incidence of adverse events in these patients. Hence, there was a need identified in those sub-populations for an initial dose lower than 500mg bid. To accommodate this need and not to complicate the SPC, the initial dose recommended has therefore been reduced generally to 375 mg bid. Moreover, the SPC specifically recommends cautious titration of the dose in all sub-groups with risk for increased exposure and adverse events. Specific warnings for patients with several risk factors have been included. The reduction of the maximum dose from 1000 mg to 750 mg bid has increased the safety margin.

Within additional risk minimisation activities, a Patient Alert Card has been introduced in order to alert patients, as well as health care professionals, on the possible contraindications, dose reductions needed, and precautions, when taken together with some other medicinal products. It also advises the patients to speak to their doctor, when they have certain specified conditions. The Patient Alert Card is therefore expected to be a useful additional tool to provide safety measures for the "real world setting".

- User consultation

In the D121 response documentation the applicant has submitted results from user testing of the PIL. The test was performed in English by Unicus Regulatory Services. 2 test rounds with 10 persons in each round were performed. No revisions of the PIL were made between the test rounds. The conclusions of the test report are clear and concise. The methodology follows the readability guideline and the results fulfil the success criteria (In round 2, only 8 of 10 could find the information regarding question 7 but when combining both rounds the criteria are fulfilled).

The applicant adequately commented on certain aspects of the test as discussed in the day 180 List of Outstanding Issues. An additional review was performed in order to discuss the changes made in the PIL during the procedure, concluding that further readability testing of the PIL was not necessary. This conclusion was endorsed by the CHMP. In conclusion, the user testing of the PIL is judged as acceptable.

**Risk-benefit assessment**

Benefits

Latixa (750 mg bid and 1000 mg bid) increased exercise duration by about 24 s and delayed the onset of angina pectoris by about 20 s in patients pre-treated with other anti-anginal agents (pivotal study CVT 3033). The design of the study was considered suboptimal regarding the base-line treatment and therefore the Applicant performed a post hoc subgroup analysis in a group of patients labelled "maximally dosed". The results in this group were similar to the results in the whole patient

population, therefore it is concluded that modest beneficial effects of ranolazine can be expected also in maximally dosed patients. Although there was no difference between the two groups in the primary efficacy endpoint, exercise duration, there was an improvement in two secondary endpoints (angina attacks and nitrogen consumption) with the 1000 mg dose compared to the 750 mg dose. Latixa also had an effect (study CVT 3037) when added to patients treated with 10 mg of amlodipine with remaining symptoms, irrespective of treatment with long acting nitroglycerin or not, resulting in a mean reduction of angina attacks (reduction by less than one attack per week) and nitroglycerin consumption. In patients with acute coronary syndrome, Latixa failed to show any differences to placebo in the primary efficacy variable (CV death, MI and recurrent ischemia) (Study CVT 3036). There was a modest significant difference in one secondary end point (mainly worsening angina/need for additional antianginal therapy). Overall, the effects on exercise duration are modest, and there is also a modest effect on other signs and symptoms of myocardial ischemia. However, Latixa represents a novel pharmacological principle and the studies inidicated that Latixa could be of value in certain patients, especially those who are intolerant to conventional treatment or those who continue to have symptoms despite maximal doses of the usual anti-anginal drugs.

Risks

The most commonly reported AEs leading to discontinuation were dizziness, nausea, and angina pectoris. However, not only do the side effects increase in number and proportion with higher concentration, but their severity is also increasing. In a tolerability study (CVT 3111), the following AEs were observed at the highest target concentrations: blurred vision, diplopia, vasovagal syncope, somnolence, and lethargy. Furthermore the QTc interval increases by a mean of 2.4 msec with every 1,000 ng/ml increase in plasma concentration. However, in a large study in patients with acute coronary syndrome (CVT 3036), there was no increase in the occurrence of severe ventricular arrhythmias in the ranolazine group compared to placebo-treated patients. Thus, at targeted therapeutic concentrations of ranolazine, the AEs were relatively benign and the frequency of SAEs was low, but this changes with higher plasma levels, with intolerable adverse events at exposure only 2-3 folds higher than the mean exposure at 1000 mg bid.

Ranolazine has a complex pharmacokinetic profile with several sub-groups at risk for increased exposure; CYP3A4 inhibitors, P-gp inhibitors, CYP2D6 inhibitors, patient with CYP2D6 poor metaboliser status (PM), patients with renal impairment or hepatic impairment. Exposure is also higher in patients in the lower weight range and in the elderly. Larger increase in exposure could be expected in patients with several risk factors for increased exposure.

Thus in summary the safety aspects of ranolzine are dominated by a high PK variability, large interaction potential, narrow therapeutic margins regarding tolerability and severe ADRs and a potential for QTc prolongation. These points add up to a drug with a narrow therapeutic window.

Benefit-risk balance

Postive findings with Latixa were:

- A relatively modest but clinically relevant effect demonstrated in a broad group of patients with stable angina pectoris
- Lack of negative haemodynamic effects

On the side of risks there was mainly a high risk for adverse events due to:

a) Narrow therapeutic margin
b) Fragile population with co-morbidities and treatment with multiple drugs
c) Complex pharmacokinetic profile with high risk for increased exposure due to drug-drug or drug-disease interactions

The concern of the CHMP was addressed during the procedure by changes of the proposed usage of Latixa with a lower dose range and contraindications and precautions, and with additional risk minimisation activities. The benefit/risk balance for Latixa is thus considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The following additional risk minimisation activities were required: see as detailed in section 2.3.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Latixa 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) was favourable and therefore recommended the granting of the marketing authorisation.