IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ranolazine Accord 750 mg prolonged-release tablets
Ranolazine
PA2315/259/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ranolazine Accord 375 mg, 500 mg & 750 mg Prolonged-release tablets, from Accord Healthcare Ireland Ltd on 19th July 2024 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).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Ranolazine Accord 750 mg prolonged-release tablets
Name(s) of the active substance(s) (INN)	Ranolazine
Pharmacotherapeutic classification (ATC Code)	C01EB18
Pharmaceutical form and strength(s)	750 mg prolonged-release tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA2315/259/003
Marketing Authorisation Holder	Accord Healthcare Ireland Ltd. Euro House Euro Business Park Little Island Cork T45 K857 Ireland
MRP/DCP No.	IE/H/1208/003/DC
Reference Member State	IE
Concerned Member State(s)	AT, CY, DE, EE, HR, IT, LT, LV

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ranolazine Accord 375 mg, 500 mg & 750 mg Prolonged-release tablets.

II.2 Drug substance

The active substance is ranolazine, an established active substance supported by an ASMF, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The finished drug products are prolonged-release tablets containing 375 mg, 500 mg and 750 mg of ranolazine.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). As a result of the warning letter issued by the FDA for the site responsible for the manufacturing of the finished product, the Applicant has committed to manage the impact of the updated risk assessment, issued by the EU lead authority, on the finished drug products Ranolazine Accord 375 mg, 500 mg and 750 mg prolonged-release tablets in line with the measures taken for other authorised products manufactured by the same site.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with <==Ph. Eur. ==> or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for prolonged-release tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ranolazine Accord 375 mg, 500 mg, 750 mg prolonged-release tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Ranexa prolonged release tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Ranolazine Accord 375 mg, 500 mg & 750 mg Prolonged-release tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Ranolazine are well known. As Ranolazine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ranolazine is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Ranexa.

For this generic application, the applicant has submitted 4 bioequivalence studies in which the pharmacokinetic profile of the test product ranolazine is compared with the pharmacokinetic profile of the reference product Ranexa.

To support the application, the applicant has submitted reports of four bioequivalence trials.

The bioequivalence studies have been performed on 750 mg single dose fasting condition,
750 mg single dose fed condition, 750 mg multiple dose fasting condition and 375 mg single dose fasting condition.

According to the EMA guideline on bioequivalence, section 6.1.2, studies to be performed in case of single unit prolonged release formulations where reference SmPC recommends intake in the fasting state or irrespective of food intake are fasting studies for all strengths unless a bracketing approach can be justified. As such, two fasting studies at highest and lowest strengths were performed.

One single dose bioequivalence study at the highest/most sensitive strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described in the Guideline are fulfilled.

For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.

For studies listed in section 6.1.1 of the guideline, studies generally required to demonstrate bioequivalence include;

- a single-dose fasting study comparing test and reference drug product
- a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference drug product.
- a multiple-dose study comparing test and reference drug product.

Based on the acceptable bio-equivalence studies for Ranolazine prolonged-release tablets 750mg, a request for waiver of bio-study on 375 mg and 500mg strength is being placed on following general requirements.

- All strengths i.e. 375 mg, 500mg and 750 mg are qualitatively and quantitatively proportional.
- Formulations of all strengths contain identical blend (and these are produced by the same manufacturing process).
- In vitro dissolution data on all the strengths confirms the adequacy of waiving additional in vivo bioequivalence testing.

The applicant has also applied for a BCS-based biowaiver, and has provided details of the relative qualitative and quantitative compositions of the strengths as well as dissolution studies in appropriate media.

The 500, 375 and 750 mg prolonged release tablets are dose proportional. The tablets have been manufactured by the same manufacturing process.

Comparable dissolution is observed between the 750 and 500 mg, and between the 500mg and 375mg strengths, all at pH 1.2, 4.5 and 6.8, supporting the waiver.

The bioequivalence studies have been performed on 750 mg single dose fasting condition, 750 mg single dose fed condition, 750 mg multiple dose fasting condition and 375 mg single dose fasting condition.

Project No. 0250-20

The study was an open label, balanced, randomized, two-sequence, two-treatment, four-period, single oral dose, fully replicate crossover, bioequivalence study in normal, healthy, adult, human subjects under fasting condition. In each study period, 27 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn/discontinued subjects to analyse the pharmacokinetic profile of the test as well as the reference product.

A washout period of 4 days was maintained between the successive dosing days.

56 non-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 to 30.0 were included in the study. Subjects did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray recordings.

Bioequivalence of the test product with that of the reference product is concluded for Cmax, if both the geometric least square mean ratio (GMR) of test to reference for Cmax and AUC0-∞ fell within the acceptance range of 80.00–125.00%.

Results

Plasma samples of all 56 subjects were analysed. Amongst the withdrawn subjects, subject nos. 1024, 1032, 1034, 1035, 1043 and 1050 completed at-least two treatment periods with one reference and one test formulation. Hence, all completer's subjects along with these six subjects (subject nos. 1024, 1032, 1034, 1035, 1043 and 1050) are included in the calculation of pharmacokinetic and statistical analysis for Ranolazine.

Subject no. 1008 (Period-III, R2) having pre-dose value is > 5% of Cmax. Hence, subject no. 1008 is excluded from period-III only in the calculation of pharmacokinetic and statistical analysis for Ranolazine. However, statistical analysis including the same has been provided for information purpose.

Total 50 subjects were included in the pharmacokinetic and statistical analysis.

Table 1: Relative bioavailability results for Ranolazine (n=50) [Excluding Subjects having pre-dose concentration > 5% of C_{max}; subject no. 1008 (period-III)]

Parameters (Units)	Geometric Least Squares Means			90 % Confidence Interval	Acceptance Criteria
	Test product-T (N=95 Observation)	Reference product- R (N=95 Observation)	Ratio (T/R)%		
lnC_{max}	892.794	929.919	96.0	89.25 - 103.27	80.00 - 125.00
$lnAUC_{0-t}$	10727.006	10266.319	104.5	95.99 - 113.73	80.00 - 125.00
$lnAUC_{0-\infty}$	10979.424	10529.406	104.3	95.79 - 113.51	80.00 - 125.00

Safety results

In general, the clinical portion of the study was completed with four AEs, out of which one (01) AE was significant. The investigational products were well tolerated by healthy subjects, as a single dose administration. There were no deaths or serious AEs reported during the conduct of the study.

Overall, the test and reference products were well tolerated by the test subjects with no AEs of significance noted.

Project No. 0251-20

The study was an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study in normal, healthy, adult, human subjects under fed condition, with a screening period of 28 days prior to IMP administration in Period-I. In each study period, 27 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn/discontinued subjects to analyse the pharmacokinetic profile of the test product as well as the reference product.

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed completely within 30 minutes.

A single oral dose (750 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered with 240 ± 02 mL of drinking water at ambient temperature in sitting posture. The IMP administration was as per the randomization schedule and under open label conditions.

A washout period of 5 days was maintained between the successive dosing days. This washout period was chosen for logistical reasons, but as it is greater than the washout period of 4 days that had been previously accepted this is not considered to be significant.

56 on-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 kg/m2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent for participation in the study were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray recordings.

Bioequivalence of the test product with that of the reference product is concluded for Cmax, if both the geometric least square mean ratio (GMR) of test to reference for Cmax and AUC0-∞ fell within the acceptance range of 80.00–125.00%.

Results

Out of the dosed 56 subjects, 52 subjects completed all the periods of the study successfully.

Plasma samples of all 56 subjects were analysed. Withdrawn Subject Nos. 1014, 1016, 1047 & 1056 were also analysed as per protocol requirement.

Total 52 subjects were included in the pharmacokinetic and statistical analysis.

Table 3: Relative bioavailability results for Ranolazine (n=52).

Parameters (Units)	Geometric Least Squares Means			90 % Confidence Interval	Acceptance Criteria
	Test product-T	Reference product- R	Ratio (T/R)%		
lnC_{max}	1016.339	951.624	106.8	100.84 - 113.11	80.00 - 125.00
$lnAUC_{0-t}$	11098.119	10629.397	104.4	98.67 - 110.49	80.00 - 125.00
$lnAUC_{0-\infty}$	11316.161	11038.806	102.5	96.45 - 108.96	80.00 - 125.00

Safety results

Five subjects reported five adverse events during the conduct of the study. Two AEs were reported in Period-I, one AE was reported in Period-II and two AEs were reported during post-study safety assessment.

Three AEs were reported in the subjects after administration of Reference Product-R and two AEs were reported in the subject after administration of Test Product-T.

All the AEs were mild in nature and the subjects were followed up until resolution of their AEs except Subject Nos. 1037 and 1055. The outcome of the AEs of these subjects was unknown as they were lost to follow-up.

Overall, the test and reference products were well tolerated by the test subjects with no AEs of significance noted.

Project No. 0252-20

The study was an open label, balanced, randomized, two-sequence, two-treatment, two-period, multiple oral dose, crossover, bioequivalence study with two consecutive profile on two consecutive days for each treatment in each period, in normal, healthy, adult, human subjects under fasting condition, with a screening period of 28 days prior to first IMP administration in Period-I.
In each study period, 43 blood samples were collected from each subject to analyse the pharmacokinetic profiles of the test product and reference products.

After fasting of at least 4 hours, a single oral dose (750 mg) of either the test product or the reference product was administered to the subjects with 240 ± 2 mL of drinking water at ambient temperature in sitting posture. The IMP administration was as per the randomization schedule and under open label conditions.

The tablet was swallowed whole without chewing or crushing.

A washout period of 4 days was maintained between the successive dosing days.

44 non-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 kg/m2 (both inclusive), who were able to understand and comply with the study procedures and having given their written informed consent for participation in the study were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray recordings.

Based on the statistical results of 90% confidence interval for the ratio of the geometric least squares means for ln-transformed pharmacokinetic parameters Cmax,ss, Cτ,ss and AUC0-τ,ss; conclusion is drawn for Test Product-T vs. Reference Product-R for Ranolazine with following considerations:

For AUC0-τ,ss: If the 90% confidence interval of geometric least squares means ratio of test to reference falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameter AUC0-τ,ss.

Results

A total of 43 subjects were dosed in Period-I of the study.

Subject Nos. 1005, 1018 and 1029 were withdrawn from the study on medical grounds in Period-I. Subject Nos. 1019 and 1040 discontinued from the study on his own accord in Period-II. Subject No. 1020 was withdrawn from the study on medical grounds in Period-II. Subject Nos. 1031 and 1034 were withdrawn from the study on the grounds of protocol non-compliance in Period-II.

In all, 35 subjects completed the clinical phase of the study successfully.

Total 35 subjects were included in the pharmacokinetic and statistical analysis.

Table 4: Relative bioavailability results for Ranolazine (n=35).

Parameters (Units)	Geometric Least Squares Means			90 % Confidence	Acceptance Criteria
	Test product-T (N = 70 Observations)	Reference product- R (N = 70 Observations)	Ratio (T/R)%		
$lnC_{max,ss}$	2229.995	2349.322	94.9	90.01 - 100.10	80.00 - 125.00
$lnC_{\tau,ss}$	1041.033^	1144.159$	91.0	82.30 - 100.59	80.00 - 125.00
$lnAUC_{0-\tau,ss}$	18685.933^	20418.200$	91.5	86.53 - 96.79	80.00 - 125.00

^N=69 observation and $N=68 observation

Safety results

six subjects reported six adverse events during the conduct of the study. Three AEs were reported in Period-I, one AE was reported in Period-II and two AEs were reported during post-study safety assessment.

Three AEs were reported in the subjects after administration of Reference Product-R and three AEs were reported in the subject after administration of Test Product-T.

Five the AEs were mild in nature and one was moderate in nature. The subjects were followed up until resolution of their AEs except Subject No. 1011whowas lost to follow-up.

Overall, the test and reference products were well tolerated by the test subjects. No unexpected AEs of significance occurred.

The applicant has presented data, which show that both Cmax and AUC are within the relevant confidence intervals.

Project No. 0254-20

The study was an open label, balanced, randomized, two-sequence, two-treatment, four-period, single oral dose, fully replicate crossover, bioequivalence study in normal, healthy, adult, human subjects under fasting condition, with a screening period of 28 days prior to IMP administration in Period-I. In each study period, 27 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn/discontinued subjects to analyse the pharmacokinetic profile of the test product as well as the reference product.

After an overnight fast of at least 10 hours, a single oral dose (375 mg) of either the test product or the reference product was administered with 240 ± 2 mL of drinking water at ambient temperature to the subjects in sitting posture. The IMP administration was as per the randomization schedule and under open label conditions.

A washout period of 5 days was maintained between the successive dosing days. This period was chosen for logistical reasons and is acceptable.

56 non-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 kg / m2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent for participation in the study were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray recordings.

Bioequivalence was assumed if the ln-transformed pharmacokinetic parameters fell within within the acceptance range of 80.00 - 125.00%. All statistical analyses for Ranolazine were performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA).

3.2.2.8.Results

A total of 56 subjects were dosed in Period-I of the study.

Subject No. 1031 was withdrawn from the study on medical grounds in Period-I. Subject No. 1050 was withdrawn from Period-II on medical grounds. Subject No. 1009 was withdrawn from Period-III on medical grounds. Subject No. 1016 was withdrawn from Period-III on the grounds of emesis. Subject No. 1020 was withdrawn from the study on the grounds of protocol non-compliance in Period-III. Subject No. 1026 discontinued from Period-III on his own accord. Subject No. 1048 discontinued from Period-III & IV on his own accord. Subject Nos. 1030 and 1036 discontinued from Period-IV on their own accord.

In all, 47 subjects completed the clinical phase of the study successfully.

Total 54 subjects were included in the pharmacokinetic and statistical analysis.

Table 5: Relative bioavailability results for Ranolazine (n=54).

Parameters (Units)	Geometric Least Squares Means			90 % Confidence Interval	Acceptance Criteria
	Test product-T (N = 103 Observations)	Reference product- R (N = 103 Observations)	Ratio (T/R)%		
lnC_{max}	591.944	592.132	100.0	94.43 - 105.83	80.00 - 125.00
$lnAUC_{0-t}$	5904.875	5795.168	101.9	95.93 - 108.23	80.00 - 125.00
$lnAUC_{0-\infty}$	6012.348	5904.202	101.8	95.88 - 108.15	80.00 - 125.00

Safety results

4 subjects reported 4 adverse events during the conduct of the study. 1 AEs were reported in Period-I, 1 AE was reported in Period-II and 2 AEs were reported during post-study safety assessment.

3 AEs were reported in the subjects after administration of Reference Product-R and 1 AE were was in the subject after administration of Test Product-T.

All the AEs were mild in nature and the subjects were followed up until resolution.

Overall, the test and reference products were well tolerated by the test subjects. No AEs of significance occurred. The applicant has presented data, which show that both Cmax and AUC are within the relevant confidence intervals.

The content of the SmPC approved during the procedure is in accordance with that accepted for the reference product.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

A summary of the well-established pharmacokinetic characteristics of Ranolazine can be found in the Summary of Product Characteristics.

IV.3 Pharmacodynamics

A summary of the well-established pharmacodynamic characteristics of Ranolazine can be found in the Summary of Product Characteristics.

IV.4 Clinical Efficacy

No new efficacy information was presented as part of this application, which is acceptable

IV.5 Clinical Safety

No new safety information was provided as part f this application, which is acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ranolazine Accord 375 mg, 500 mg & 750 mg Prolonged-release tablet.

Safety specification

Important identified risks	• QT prolongation
Important potential risks	• Myasthenia syndrome

	• Cardiac arrhythmias
Missing information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

The test and reference products are considered to be bioequivalent.

V. OVERALL CONCLUSIONS

Ranolazine Accord 375 mg, 500 mg & 750 mg Prolonged-release tablets are generic forms of Ranexa. Ranexa is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Ranolazine Accord Prolonged-release tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

30.04.2029