COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lazela 375 mg, 500 mg and 750 mg, prolonged-release tablets

(ranolazine)

NL/H/5343/001-003/DC

Date: 20 September 2022

This module reflects the scientific discussion for the approval of Lazela 375 mg, 500 mg and 750 mg, prolonged-release tablets. The procedure was finalised at 12 May 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lazela 375 mg, 500 mg and 750 mg, prolonged-release tablets, from Demo SA Pharmaceutical Industry.

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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ranexa 375 mg, 500 mg and 750 mg, prolonged-release tablets which has been registered in the EEA by Menarini International Operations Luxembourg S.A. since 9 July 2008 via a centralised procedure (EMEA/H/C/000805).

The concerned member state (CMS) involved in this procedure was Greece.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

All three strengths of Lazela tablets are white, oblong, convex and film-coated.

- The 375 mg tablets contain 375 mg of ranolazine and have “375” embossed on one side.
- The 500 mg tablets contain 500 mg of ranolazine and have “500” embossed on one side.
- The 750 mg tablets contain 750 mg of ranolazine and have “750” embossed on one side.

Each strength of tablets is packed in PVC/PVDC/aluminium blisters.

The excipients for all tablet strengths are:

- *Tablet core* - microcrystalline cellulose 101 (E460), methacrylic acid-ethyl acrylate copolymer (1:1), sodium hydroxide (E524), hypromellose E50 (E464), magnesium stearate (E470b).
- *Film-coating system Aqua Polish P white* - hypromellose E5 and E15 (E464), hydroxypropylcellulose (E463), macrogol 8000 (E1521), titanium dioxide (E171).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is ranolazine, an established active substance not described in the European Pharmacopoeia or the British Pharmacopoeia. A draft monograph has been published in the United States Pharmacopeia (USP). The active substance is a white to off-white crystalline powder. It is soluble in dichloromethane and methanol, sparingly soluble in tetrahydrofuran and acetonitrile, and slightly soluble in toluene. The solubility in aqueous solutions is pH dependent with the highest solubility at low pH. The drug substance is present as a racemate and polymorphic form I is consistently used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of four steps with three isolated intermediates. Acceptable specifications have been adopted for the starting materials, solvents and reagents. The structure of the active substance has been adequately characterised. Information has been provided on specified and other possible organic impurities, residual solvents, elemental impurities as well as on potentially genotoxic impurities.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is largely based on the USP draft monograph for ranolazine. The specification of the drug product manufacturer is in line with the specification of the ASMF holder and contains additional requirements for particle size distribution and microbiological purity. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided on six full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for eleven production scaled batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months) which is in accordance with applicable European guidelines. Two of the batches were reprocessed and three batches were micronised. The tested parameters are considered to indicate stability sufficiently. No significant changes or specific trends are seen at both storage conditions. The active substance is not sensitive to light and remains a racemate during storage. Micronisation does not influence the polymorphic form and the impurity levels. On the basis of the provided stability data, the claimed re-test period of 60 months is acceptable. Based

on the provided stability data no storage precautions are needed, however the instruction from the ASMF holder to store below 25°C has been accepted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The choices of packaging and manufacturing process are justified in relation to the innovator. The proposed QC dissolution method is in line with the USP draft monograph for ranolazine. The discriminating power of the QC dissolution method has been adequately demonstrated. In total five bioequivalence studies were performed. Four studies were done with the 750 mg tablets, one study under fed conditions, one multiple-dose study under fasted conditions and two single-dose studies were done under fasted conditions. One single-dose study was conducted with the 375 mg tablets under fasted conditions. A biowaiver of strength was requested for the 500 mg strength and for the 375 mg strength under fed conditions and for the multiple-dose study.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. The manufacturing process consists of a wet granulation of pre-weighted ingredients in purified water, followed by drying, sizing, blending, tableting, film-coating and packaging. The manufacturing of the drug product is considered non-standard (modified release preparation). The description of the manufacturing process is sufficiently detailed and the proposed holding time is acceptable.

Control of excipients

The excipients comply with Ph.Eur. requirements. Their specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, length of the tablet, average mass of one tablet, uniformity of mass of single tablet, identification of the drug substance, chromatographic purity, dissolution, dissolution, assay and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation concerning the presence of nitrosamine impurities in the product has been provided in accordance with applicable European guidelines. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three commercial batches per strength, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three commercial batches per strength stored under long-term stability conditions at 25°C/60% RH (up to 36 months),

30°C/75% RH (up to 36 months) and 40°C/75% RH (6 months). This in accordance with applicable European guidelines. The drug product was packed in PVC/PVDC blister with aluminium lidding foil. All results have been found within the proposed limits and no significant upward or downward trend has been observed. Photostability studies have demonstrated that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 30 months. No specific storage conditions need to be included in the SmPC or on the label. The bulk product has been found stable for six months at NMT 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lazela has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lazela is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ranexa which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ranolazine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted five bioequivalence studies which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted five bioequivalence studies in which the pharmacokinetic profile of the test product Lazela 375 mg and 750 mg, prolonged-release tablets (Demo SA Pharmaceutical Industry, Greece) is compared with the pharmacokinetic profile of the reference product Ranexa 375 mg and 750 mg, prolonged-release tablets (Menarini International Operations Luxembourg, Luxembourg).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver of strength was requested for the 500 mg strength and for the 375 mg strength under fed conditions and for the multiple-dose study. The following conditions are fulfilled:

- The products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- Appropriate *in vitro* dissolution data are available for all strengths at three pH values.
- The three strengths are dose proportional.

This is in line with the requirements of the EMA Guideline on Bioequivalence.

Bioequivalence studies

Four bioequivalence studies have been conducted under fasted conditions; one study was done under fed conditions. Ranolazine may be taken without reference to food intake. Therefore, further food interaction studies are not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical methods of all studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study 1 (single dose, fasting, 750 mg tablet)
Design
A single-dose, randomised, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 52 healthy adult subjects aged 19-55 years. In the study 20 males and 32 females were included. Each subject received a single dose (750 mg) of one of the two ranolazine formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected at pre-dose and at 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of the products. The design of the study is acceptable.

Results
All 52 subjects completed the study and were eligible for pharmacokinetic analysis. No serious adverse event occurred.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ranolazine 750 mg under fasted conditions.

Treatment N=52	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	10600 ± 900	11200 ± 6900	760 ± 390	6.5 (2.2 – 28.0)
Reference	11200 ± 6200	11700 ± 6200	890 ± 390	5.5 (2.0 – 28.0)
***Ratio (90% CI)**	0.95 (0.89 – 1.02)	0.96 (0.89 – 1.03)	0.87 (0.798 – 0.936)	--
CV (%)	22.0	22.0	24.3	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were inside the normal range of acceptability (0.80 – 1.25). However, the rate of absorption of the test and reference products are not bioequivalent, as the 90% confidence interval calculated for C_{max} (i.e. 0.798 – 0.936) is outside the normal range of acceptability (0.80 – 1.25). When compared to the reference formulation the data from the test formulation showed a higher occurrence of double peaks which might imply a difference in product performance. In order

to resolve this a new bioequivalence study was performed. This study (study 2) is described below and was done under the same fasting conditions with the 750 mg tablet.

Study 2 (single dose, fasting, 750 mg tablet)

Design

A single-dose, randomised, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 67 healthy adult subjects aged 18-54 years. In the study 44 males and 23 females were included. Each subject received a single dose (750 mg) of one of the two ranolazine formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were two dosing periods, separated by a washout period of fourteen days. Blood samples were collected at pre-dose and 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 28.0, 32.0, 36.0 and 48.0 hours after drug administration of the products. The design of the study is acceptable.

Results

During the washout period three subjects withdrew from the study for personal reasons therefore, 64 subjects completed the study and were eligible for pharmacokinetic analysis. No serious adverse event occurred.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ranolazine 750 mg under fasted conditions.

Treatment N=64	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	10400 ± 5880	10640 ± 6260	880 ± 350	4.5 (2.0-12.0)
Reference	10480 ± 6280	10650 ± 6310	860 ± 420	5.5 (1.0-16.0)
***Ratio (90% CI)**	0.99 (0.93 – 1.06)	0.99 (0.93 – 1.06)	1.05 (0.97 – 1.14)	--
CV (%)	22.5	22.7	29.2	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**Ln-transformed values*

Pooled data of study 1 and study 2

The EMA bioequivalence guideline describes the following on pooling: "*If for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole. The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored. The MAH should thoroughly discuss the results and justify the claim that bioequivalence has been demonstrated. Alternatively, when*

relevant, a combined analysis of all studies can be provided in addition to the individual study analyses." Therefore data of the two 750 mg fasting studies were pooled and statistically evaluated.

The pooling of the data in a more conservative approach (Bonferroni adjustment) was taken into account. An ANOVA was used including the study as factor as well as sequence, period treatment. The model is a fixed model with Group + Sequence + Sequence*Group + Subject(Sequence*Group) + Period(Group) + Treatment, in this model group correspond to study. The results of this approach are presented in table 3.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, (median, range)) of ranolazine 750 mg under fasted conditions. Results of study 1 and study 2 pooled.

Treatment N=116	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)
Test	9160.3	9539.2	744.7
Reference	9404.4	9761.4	773.0
***Ratio (90% CI)**	0.97 (0.92 – 1.03)	0.98 (0.92– 1.03)	0.96 (0.9– 1.3)
CV (%)	22.25	22.31	27.91

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
CV coefficient of variation

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Pooled data showed overall hat bioequivalence could be proven for both AUC and C_{max}.

Study 3 (single dose, fed conditions, 750 mg tablet)

Design

A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fed conditions in 60 healthy adult subjects aged 18-55 years. In the study 32 males and 28 females were included. Each subject received a single dose (750 mg) of one of the two ranolazine formulations. The tablet was orally administered with 200 ml water 30 minutes after start of intake of a high fat, high calorie meal. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected at pre-dose ,1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 16.0, 24.0, 28.0 and 36.0 hours after administration of the products. The design of the study is acceptable.

Results

Two subjects were withdrawn from the study in period I because of QTc interval increases above their D-1 baselines. In total 58 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ranolazine 750 mg under fed conditions.

Treatment N=58	AUC_{0-t} (Ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	9400 ± 4600	10400 ± 4600	740 ± 320	4.5 (2.0-16.0)
Reference	9300 ± 4700	10900 ± 5200	750 ± 310	5.5 (2.5-12.0)
***Ratio (90% CI)**	1.01 (0.97 – 1.05)	0.96 (0.89 – 1.03)	0.98 (0.92– 1.04)	--
CV (%)	13.1	23.6	20.7	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Study 4 (multiple doses, fasted conditions, 750 mg tablets)

Design

A multiple-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 60 healthy subjects, aged 22-53 years. In the study 35 males and 25 females were included. Each subject received a 750 mg dose (1x 750 mg) of one of the ranolazine formulations every 12 hours for 5 days. The tablet was orally administered with 200 ml water after an overnight fast. Subjects received identical standard meals throughout the study period. There were two dosing periods, separated by a washout period of 16 days. Blood samples were collected before presumed reaching steady state, at -96.08 (day 1), -72.08 (day 2), -48.08 (day 3), -36.08 (day 3), -24.08 (day 4), -12.08 (day 4) and at -0.08 (day 5) hours. Then, after reaching steady state, the sampling was provided after dosing on Day 5, at 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00 and 12.00 hours post-dose. The design of the study is acceptable.

Results

During period II one subject was withdrawn as the subject was not able to swallow the formulation and two subjects withdrew for personal reasons. Therefore, 57 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD,(median, range)) of ranolazine after multiple administrations of Ranolazine 750 mg prolonged release tablets under fasting conditions.

Treatment N=57	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	C_{tau} (ng/ml)
Test	13950 ± 8830	1530 ± 840	930 ± 690
Reference	14470 ± 8570	1630 ± 830	910 ± 680
***Ratio (90% CI)**	0.93 (0.86 – 1.02)	0.91 (0.84 – 0.99)	0.96 (0.83 – 1.11)
CV (%)	27.8	26.2	48.3

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{tau} concentration at τ time point
CV coefficient of variation

Study 5 (single dose, fasted conditions, 375 mg tablet)

Design

A single-dose, randomised, two-period, two-treatment crossover bioequivalence study was carried out under fasted conditions in 60 healthy subjects, aged 21-54 years. In the study 30 males and 30 females were included. Each subject received a single dose (375 mg) of one of the two ranolazine formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected at pre-dose (0) ,1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 28.0, 32.0, 36.0 and 48.0 hours after administration of the products. The design of the study is acceptable.

Results

In the washout period three subjects withdrew from the study. One subject due to personal reasons and two subjects withdrew from the study due to upper respiratory tract infections. In total 57 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ranolazine 375 mg under fasted conditions.

Treatment N=57	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	5520 ± 3420	5590 ± 3430	630 ± 350	5.5 (2.5 -12.0)
Reference	5580 ± 3660	5890 ± 4460	540 ± 270	5.0 (2.0 – 8.0)
***Ratio (90% CI)**	1.01 (0.95 – 1.07)	0.99 (0.93 – 1.05)	1.13 (1.04 – 1.24)	--
CV (%)	17.7	18.3	28.2	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 for four of the five studies. The pooled data of study 1 and study 2 also proved bioequivalence. Based on the submitted bioequivalence studies Lazela 750 mg, prolonged-release tablets are considered bioequivalent with Ranexa 750 mg, prolonged-release tablets. For the 375 mg tablets bioequivalence was proven under single-dose and fasted conditions.

The results of the bioequivalence studies can be extrapolated to the lower strength of 500 mg and the 375 mg strength under fed conditions and for the multiple-dose study.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Lazela.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	- QT prolongation

Important potential risks	- Myasthenic syndrome - Cardiac arrhythmias
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Ranexa. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Polish. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lazela with the reference

product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 May 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse