COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Darifenacin Aristo 7.5 mg prolonged-release tablets
(darifenacin hybromide)

NL/H/4424/003/DC

Date: 14 September 2021

This module reflects the scientific discussion for the approval of Darifenacin Aristo 7.5 mg prolonged-release tablets. The procedure was finalised at 23 March 2021. 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 Darifenacin Aristo 7.5 mg prolonged-release tablets, from Aristo Pharma GmbH.

The product is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with overactive bladder syndrome.

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 Emselex 7.5 mg, prolonged-release tablets which has been registered by Novartis Pharma AG on 22 October 2004 in Europe by a centralised procedure (EMEA/H/C/000554). The marketing authorisation was later transferred to Merus Labs Luxco II S.à R.L., the current marketing authorisation holder.

Darifenacin Aristo 7.5 mg is a line-extension from Darifenacin Aristo 15 mg prolonged-release tablets, which has been registered since 21 October 2019 via procedure NL/H/4414/002/DC.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom (Northern Ireland).

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

II. QUALITY ASPECTS

II.1 Introduction

Darifenacin Aristo is a white to off-white, round, biconvex, film-coated tablet that is embossed with “7.5” on one side. It contains as active substance 7.5 mg of darifenacin (as hydrobromide).

The film-coated tablets are packed in PVC/PVdC-Al blisters in carton.

The excipients of the tablet core are calcium hydrogen phosphate (E341(ii)), hypromellose (E464) and magnesium stearate (E470b). The excipients of the film-coating are hypromellose (E464), titanium dioxide (E171), macrogol and talc (E553b).

II.2 Drug Substance

The active substance is darifenacin hydrobromide, an established active substance not described in any Pharmacopoeia. The active substance is a white to off-white crystalline powder and is practically insoluble in water, independent of pH. Darifenacin hydrobromide contains one asymmetric carbon which exists in S-isomeric form and exhibits polymorphism. The anhydrous crystalline form is used for the drug product, which is identical to the form used in the reference product.

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 of drug substance

The manufacturing process consists of eight stages, with six chemical transformations and two purification steps. In the last step, the material is crystallised. No heavy metal catalysts or class 1 solvents have been used in the synthesis. The drug substance may be micronised. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification of the MAH is based on the specifications of the ASMF holder, with additional requirements for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scale batches and three full scale batches stored at 25°C/60% RH (60 months pilot scale, 48 months full scale) and 40°C/75%RH (six months). The stability studies are in accordance with applicable European guidelines. Little change was observed for any of the parameters tested in the stability studies, both under six months accelerated conditions and under 60 months long term conditions. Therefore, a retest period could be granted of 60 months when stored in a sealed double polyethylene bag that is placed in a sealed triple laminated bag in a HDPE container.

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 excipients were selected based on the excipients used in the reference product, and their choice has been justified. To obtain a drug product with a similar prolonged release dissolution as the reference product, the ratio between the diluent (calcium hydrogen phosphate) and the rate controlling polymer (hypromellose) was optimised, as well as the amount of lubricant. The choices of the packaging (PVC/PVdC-Alu blisters) and manufacturing process have been justified. Comparative dissolution profiles of the drug product and reference product were determined in different media. The active substance showed similar dissolution profiles in the test product compared to the reference product in all tested media. Furthermore, three bioequivalence studies have been been conducted under fed (single dose) and fasting conditions (single and multiple dose), which will be discussed in section IV.

Manufacturing process

The manufacturing process consists of preparation of the pre-lubrication blend, preparation of the final compression blend, tableting, coating, and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients are described in the Ph. Eur., with exception of the coating (Opadry White), which complies with in-house specifications. These 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 description, identity, assay, uniformity of dosage units, dissolution, related substances, and microbial contamination. The specifications are acceptable. The release and shelf-life limits are identical, except for total impurities. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Although a clear increase is seen in total impurities, the increase is small. All other parameters tested are stable for 36 months at long-term storage conditions and for six months under accelerated conditions. Further, a photostability study was conducted, which showed that the drug product is stable when exposed to light. On basis of

the data submitted, a shelf life was granted of 48 months. The labelled storage conditions are: “This medicinal product does not require any special storage conditions”.

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 Darifenacin Aristo 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 Darifenacin Aristo 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 Emselex 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

Darifenacin 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Darifenacin Aristo 7.5 mg prolonged-release tablets (Aristo Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Emselex 7.5 mg, prolonged-release tablets (Merus Labs Luxco II S.a R.L., Luxembourg). The three bioequivalence studies performed were a single dose fasting study, a single dose study under fed conditions and a multiple dose fasting study. Since Darifenacin Aristo is a prolonged-release tablet, submission of these types of bioequivalence studies was considered adequate. The choice of the reference product in the bioequivalence studies has been justified by a comparison of dissolution results and compositions between the drug product and reference product. The formula and preparation of the bioequivalence batches were identical to the formula proposed for marketing.

Bioequivalence studies

Study designs

- Single-dose fasting study
  A single-dose, randomised, two-way, two-period, crossover bioequivalence study was carried out under fasting conditions in 58 healthy male subjects, aged 19 - 43 years. Each subject received a single dose (7.5 mg) of one of the two darifenacin formulations. The tablet was orally administered with 240 ml water after an overnight fast. The wash-out period was ten days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 30, 36, 48, 72, 96 and 120 hours after administration of the products. The design of the study was acceptable.

- Single-dose study under fed conditions
  A single-dose, randomised, two-way, two-period, crossover bioequivalence study under fasting conditions was conducted under 58 healthy male subjects, aged 20 - 44 years. Each subject received a single dose (7.5 mg) of both darifenacin formulations. The tablet was orally administered with 240 ml water within 30 min after intake of a high fat high caloric meal. The wash-out period was ten days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 30, 36, 48, 72, 96 and 120 hours after administration of the products. The design of the study was acceptable.

- Multiple-dose fasting study
  A multiple-dose, two-treatment, three-period, three-sequence, randomised, crossover bioequivalence study under fasting conditions was carried out under 72 healthy male subjects, aged 20 - 43 years. Each subject received daily, for a period of nine days, a single dose (7.5 mg) of one of the active substance formulations under fasting conditions. The tablets were orally administered with 240 ml water. The study was a replicate designed study, in which the reference product was given in two of the three

periods. The wash-out period between the periods was nine days. In each period, blood samples were taken pre-dose at day 6, 7, 8 and 9 and at day 9 at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 hours after administration of the products. The design of the study was acceptable.

Analytical/statistical methods

The analytical method used in all bioequivalence studies has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable as well.

Results

- Single-dose study under fasting conditions

Out of 58 subjects, 55 subjects were eligible for pharmacokinetic analysis. Three subjects were withdrawn from the study due to adverse events (diarrhoea, one subject; vomiting, one subject) and absence from the study centre for period II (one subject).

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

Treatment N=55	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	52 ± 49	53 ± 50	2.64 ± 1.68	6.5 (2.0 – 24.0)	7.0 ± 2.8
Reference	52 ± 32	53 ± 32*	2.39 ± 1.12	6.5 (5.0 – 24.0)	7.8 ± 3.7*
****Ratio (90% CI)**	0.93 (0.85 – 1.01)	0.92 (0.84 – 1.01)	1.05 (0.96 – 1.14)	--	--
CV (%)	28.9	29.1	26.6	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation
* n=54: Kel could not reliable evaluated for one of the subjects in Period I as the subject did not exhibit log-linear relationship in the terminal elimination phase
** *ln-transformed values*

- Single-dose study under fed conditions

  Out of 58 subjects, 45 subjects were eligible for pharmacokinetic analysis. 13 subjects were withdrawn from the study due to personal reasons (one subject), adverse events (vomiting, nine subjects; diarrhoea, two subjects) and due to absence from the study centre (one subject).

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

Treatment N=45	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	56 ± 28	57 ± 28	4.09 ± 1.96	5.5 (2.0 – 16.0)	6.9 ± 2.3
Reference	54 ± 32	55 ± 32	3.92 ± 2.05	5.5 (2.0 – 20.0)	6.9 ± 2.3
***Ratio (90% CI)**	1.02 (0.95 – 1.09)	1.02 (0.95 – 1.09)	1.05 (0.96 – 1.15)	--	--
CV (%)	19.4	19.2	25.6	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation
*	*ln-transformed values*

- Multiple-dose study under fasting conditions

Out of 72 subjects, 69 subjects were eligible for pharmacokinetic analysis. Two subjects withdrew from the study due to personal reasons and one subject was withdrawn due to an adverse event (vomiting).

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of darifenacin under fasted conditions.

Treatment N=69 (test) and 138 (reference)	$AUC_{0-\tau,ss}$ (ng.h/ml)	$C_{max,ss}$ (ng/ml)	$C_{\tau,ss}$ (ng/ml)	$t_{max,ss}$ (h)	Fluctuation (%)
Test	67 ± 45	4.24 ± 2.49	1.98 ± 1.78	5.5 (2.0 – 22.0)	112 ± 46
Reference	67 ± 45	4.23 ± 2.67	1.93 ± 1.66	5.5 (1.0 – 24.0)	107 ± 42
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	1.02 (0.97 – 1.08)	0.99 (0.87 – 1.12)	--	--
CV (%)	21.6	21.1	54.2	--	--

$AUC_{0-\tau,ss}$	area under the plasma concentration-time curve from time zero to end of dosing interval
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{\tau,ss}$	concentration at the end of dosing interval at steady state
$t_{max,ss}$	time for maximum concentration
CV	coefficient of variation
*	*ln-transformed values*

Conclusion on bioequivalence studies

In all three bioequivalence studies the calculated 90% confidence intervals were within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Darifenacin Aristo 7.5 mg prolonged release tablets is considered bioequivalent with Emselex 7.5 mg prolonged release tablets after single dosing under fasting and fed conditions, and after multiple dosing (steady state).

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 Darifenacin Aristo.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
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 Emselex. No new clinical studies were conducted. The MAH demonstrated through three bioequivalence studies 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 test consisted of: a pilot test with three 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

Darifenacin Aristo 7.5 mg prolonged-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Emselex 7.5 mg, prolonged-release tablets. Emselex 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 Darifenacin Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 March 2021.

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
NL/H/4424/ 003/IB/003	Type IB: C.I.2.a - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product; Implementation of change(s) for which no new additional data is required to be submitted by the MAH	SmPC, PL	9-7-2021	Approval	