COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Darifenacine Aristo 15 mg prolonged release tablets

# (darifenacine hydrobromide)

# NL/H/4424/002/DC

# Date: 5 November 2019

**This module reflects the scientific discussion for the approval of Darifenacine Aristo 15 mg prolonged release tablets. The procedure was finalised at 11 September 2019. 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 |
| 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 Darifenacine Aristo 15 mg prolonged release tablets from Aristo Pharma GmbH.

The product is indicated for the 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 15 mg prolonged release tablets which has been centrally registered (EMEA/H/C/000554) in the EEA by Novartis Pharma AG since 22 October 2004 (original product). The marketing authorisation was later transferred to Merus Labs Luxco II S.à R.L., the current marketing authorisation holder.

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Sweden and the United Kingdom.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Darifenacine Aristo is a light peach coloured, round, biconvex prolonged-release film-coated tablet.

And contains as active substance 15 mg of darifenacine, as 17.846 mg of darifenacine hydrobromide.

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

The excipients are:
*Tablet core* - calcium hydrogen phosphate (E341(ii)), hypromellose (E464), magnesium stearate (E470b).
*Film-coating* - hypromellose, titanium dioxide (E171), macrogol, talc (E553b), yellow iron oxide (E172), red iron oxide (E172).

## II.2 Drug Substance

The active substance is darifenacine 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. Darifenacine hydrobromide contains one asymmetric carbon which exists in S-isomeric form; and exhibits polymorphism, the anhydrous crystalline form is used, which is identical to the form used in the reference product.

The Active Substance Master File (ASMF) procedure is used by both manufacturers 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 eight stages, with six chemical transformations and two purification steps. No heavy metal catalysts or class 1 solvents have been used in the synthesis. The drug substance may be micronized. The active substance has been adequately characterized. The specifications for the used starting materials, intermediates, solvents and reagents are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. It includes additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches from manufacturer I and five batches from manufacturer II.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 30°C/65% RH (60 months) and 40°C/75% RH (6 months) by manufacturer I; and 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 (6 months) by manufacturer II.
For both drug substance manufacturers, little change is seen for any of the parameters tested in the stability studies, under 6 months accelerated conditions and 60 months long term conditions. Based on the data submitted, a retest period could be granted of 60 months for both manufacturers.

## 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 excipients were selected based on the excipients used in the reference product. To obtain a drug product with a similar prolonged release dissolution as the reference product the ratio between the diluent and the rate controlling polymer was optimised, as well as the amount of lubricant. The choices of the packaging and manufacturing process have been justified. The pharmaceutical development of the product has been adequately performed.

Three bioequivalence studies have been performed; two single dose studies (one in fed, and one in fasted state) and one multiple dose study. The provided CoA's show that the difference in assay is less than 5%. The composition of the batch of Darifenacin 15 mg prolonged release tablets used in the pivotal bioequivalence is the same as proposed for marketing. Comparative dissolution profiles were determined in 0.1N HCl (quality control medium), pH 4.5 acetate buffer and pH 6.8 phosphate buffer for the 15 mg strength of the test product and Emselex 15 mg prolonged-release tablets. The active ingredient darifenacine shows similar dissolution profiles in the test product compared to the reference product in all tested media.

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 Opadry White and Opadry Yellow which comply 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 release and shelf-life requirements/limits are identical, except for the limit for total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three full scale batches of each strength, stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

All results stayed well within specification. All other parameters tested are stable over a period of 36 month long term storage and 6 months storage under accelerated conditions. Based on these results a shelf life was granted of 42 months, without any special storage condition.

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 Darifenacine 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 Darifenacine 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

Darifenacine 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 15 mg prolonged-release tablets (Aristo Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Emselex 15 mg prolonged-release tablets (Merus Labs Luxco S.à R.L., Germany):

- A single-dose fasting study comparing test and reference drug product
- A single-dose fed study using a high-fat meal comparing test and reference drug product
- A multiple-dose study comparing test and reference drug product

The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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

Bioequivalence studies
***Single dose study under fasted conditions 766/16***
*Design*
A single dose, 2-way, 2-period, randomised, crossover bioequivalence study was carried out under fasted conditions in 66 healthy male subjects, aged 18-43 years. Each subject received a single dose (15 mg) of one of the two darifenacine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, with a wash-out period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 30, 36, 48, 72, 96 and 120 hours after administration of the products.

The study design is acceptable.

*Results*
Eight subjects were withdrawn or withdrew from the study. Therefore, 58 subjects were eligible for pharmacokinetic analysis.

In addition for one subject no plasma concentrations were observed after administration. It is sufficiently justified to exclude this subject from the statistical analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of darifenacine 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) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 116 ± 76 | 118 ± 77 | 5.5 ± 2.6 | 6.5 (4.0 – 25.0) | 7.7 ± 4.5 |
| **Reference** | 127 ± 96 | 129 ± 96 | 5.5 ± 2.8 | 8.0 (5.0 – 27.0) | 7.9 ± 4.4 |
| ***Ratio (90% CI)** | 0.92 (0.85 – 1.00) | 0.92 (0.84 – 1.00) | 0.99 (0.92 – 1.07) | -- | -- |
| **CV (%)** | 28.0 | 27.4 | 23.8 | -- | -- |

**$AUC_{0-\infty}$** 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*

***Single dose study under fed conditions 767/16***
*Design*
A single dose, 2-way, 2-period, randomised, crossover bioequivalence study was carried out under fasted conditions in 66 healthy male subjects, aged 20-45 years. Each subject received a single dose (15 mg) of one of the two darifenacine formulations. The tablet was orally administered 30 minutes after the start of intake of a high fat, high caloric breakfast in solid form with 240 ml water. The breakfast contained approximately 150, 250 and 500-600 kcal from protein, carbohydrate, and fat, respectively. There were two dosing periods, with a wash-out period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 30, 36, 48, 72, 96 and 120 hours after administration of the products.

The study design is acceptable. A single dose, crossover study under fasting and fed conditions to assess bioequivalence is considered adequate.

*Results*
Seven subjects were withdrawn or withdrew from the study. Therefore, 59 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=59 | $AUC_{0-t}$ (ng.h/ml) | $AUC_{0-\infty}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 143 ± 97 | 144 ± 97 | 9.3 ± 5.3 | 5.5 (2.0 – 22.0) | 7.4 ± 3.3 |
| **Reference** | 141 ± 94 | 142 ± 94 | 9.6 ± 5.5 | 6.5 (2.0 – 17.0) | 7.2 ± 2.2 |
| ***Ratio (90% CI)** | 0.98 (0.92 – 1.04) | 0.98 (0.92 – 1.04) | 0.99 (0.91 – 1.08) | -- | -- |
| **CV (%)** | 20.3 | 20.5 | 26.8 | -- | -- |

**$AUC_{0-\infty}$** 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 762/17***
*Design*
A multiple dose, 2-way, 2-period, randomised, crossover bioequivalence study was carried out under fasted conditions in 58 healthy male subjects, aged 20-43 years. Each subject received for seven days a single dose (15 mg) of one of the two darifenacine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There was no wash-out period.

Blood samples were collected pre-dose and at 4, 5 and 6, and at day 7 at 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 and 24 hours after administration of the products.

The study design is acceptable. Between the study periods no washout period was included, which is acceptable, considering that at day 7 in each period the pharmacokinetics were evaluated. This is sufficient long to prevent carry over from the previous period.

*Results*
Four subjects were withdrawn or withdrew from the study. Therefore 54 subjects were eligible for pharmacokinetic analysis.

**Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)**

| Treatment N=54 | $AUC_\tau$ (ng/ml/h) | $C_{max,ss}$ (ng/ml) | $C_{min,ss}$ (ng/ml) | $C_\tau$ (ng/ml) | $C_{avg}$ (ng/ml) | $t_{max}$ (h) | PTF% (%) |
|---|---|---|---|---|---|---|---|
| **Test** | 141 ± 76 | 8.7 ± 4.4 | 3.4 ± 2.2 | 4.5 ± 3.4 | 5.9 ± 3.3 | 5.5 (2.0 – 20.0) | 96 ± 38 |
| **Reference** | 138 ± 85 | 8.3 ± 4.7 | 3.7 ± 2.9 | 4.7 ± 3.9 | 5.8 ± 3.5 | 5.75 (2.0 – 22.0) | 88 ± 36 |
| ***Ratio (90% CI)** | 1.02 (0.95 – 1.10) | 1.06 (0.99 – 1.13) | -- | 0.93 (0.80 – 1.09) | -- | -- | -- |
| **CV (%)** | 22.7 | 20.4 | -- | 50.5 | -- | -- | -- |

**$AUC_\tau$** area under the plasma concentration-time curve over the dosing interval
**$C_{max}$** maximum plasma concentration
**$C_{min}$** minimum plasma concentration
**PTF%** fluctuation index
**CV** coefficient of variation

Conclusion on bioequivalence studies

The 90% confidence intervals calculated are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Darifenacin Aristo 15 mg prolonged-release tablets is considered bioequivalent with Emselex 15 mg prolonged-release tablets.

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**

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|---|---|
| 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 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 test consisted of: a pilot test with three participants, followed by two rounds with ten 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 PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Darifenacine Aristo 15 mg prolonged release tablets has a proven chemical-pharmaceutical quality and is a generic form of Emselex 15 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 Darifenacine Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 September 2019.

## 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 |
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