COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mebeverine Aristo 200 mg modified release capsules, hard

(mebeverine hydrochloride)

NL/H/4476/001/DC

Date: 14 November 2019

This module reflects the scientific discussion for the approval of Mebeverine Aristo 200 mg modified release capsule, hard. The procedure was finalised at 26 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 Mebeverine Aristo 200 mg modified release capsules, hard from Aristo Pharma GmbH.

The product is indicated for the symptomatic relief of irritable bowel syndrome in adult patients.

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 Colofac retard 200 mg capsules which has been registered in Austria by BGP Products GmbH since 27 January 2000 (original product). In the Netherlands, the quantitative composition of this product is the same as Duspatal Retard 200 mg, modified release capsules which has been registered by Abbott B.V. since 12 August 1987 through a national procedure.

The concerned member states (CMS) involved in this procedure were Austria, Germany, Denmark, Poland, and Portugal.

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

II. QUALITY ASPECTS

II.1 Introduction

Mebeverine Aristo is a hard modified-release capsule. The capsules have a creamy white body and cap. They are filled with white to off white spherical pellets. Each capsule contains as active substance 200 mg of mebeverine hydrochloride.

The product is packed in PVC/PVDC-Al blisters.

The excipients are:
Core - sugar spheres (sucrose, maize), povidone (E1201), hypromellose (E464)
Coating - ethyl cellulose N-45, macrogol 6000 (E1521), magnesium stearate (E470b)
Capsule - gelatin, titanium dioxide (E171)

II.2 Drug Substance

The active substance is mebeverine hydrochloride, an established active substance described in the British and European Pharmacopoeia (Ph.Eur.). The active substance is very soluble in water and in methylene chloride, and freely soluble in ethanol (96%). It has a pKa value of 10.7. Mebeverine hydrochloride has a chiral carbon in its chemical structure; hence it can exhibit optical isomerism, however, the substance is produced as a racemate. It has been demonstrated that the same polymorphic form is manufactured consistently.

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 active substance is manufactured from two key intermediates. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, intermediates, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. 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 commercial batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (six months). Additionally, stability data of three commercial batches of mebeverine hydrochloride (six months accelerated and 24 months long-term stability) were also provided. The drug substance remained stable. There are no significant changes or unexpected results observed. Based on the available stability data, a retest period could be granted of 60 months when stored in a well closed container at room temperature.

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. Several development studies have been performed related to the characterization of reference product, choice and quantity of the excipients,

choice of the manufacturing formula and process and *in vitro* comparative study with the reference product.

Three bioequivalence studies versus the EU reference product Colofac Retard have been performed. Batches used in the bioequivalence studies were manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been adequately described and 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.

Control of excipients

All excipients comply with the Ph.Eur., except for the empty hard gelatin capsule. 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 appearance, identity, average fill weight, uniformity of fill weight, uniformity of dosage units, water content, dissolution, related substances, assay, residual solvents and microbial quality. 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 for three full scaled batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. At long term and intermediate conditions the product remains stable, there are no specific trends or out of specification results obtained. However, at accelerated conditions, significant changes and out of specification results are obtained after six months for dissolution, individual unknown impurity and total impurities.
On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage condition is “Store below 30°C in the original package in order to protect from moisture”.

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 Mebeverine 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 Mebeverine 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 Colofac retard 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

Mebeverine hydrochloride 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 Mebeverine Aristo 200 mg modified release capsules, hard (Aristo Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Colofac retard 200 mg capsules (Abbott Products GmbH, Austria).

Reference 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 method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The MAH analysed four metabolites (veratric acid, mebeverine acid, and desmethyl mebeverine acid, desmethyl mebeverine alcohol). Veratric acid is considered the pivotal analyte for bioequivalence evaluation.

IV.2.1 Single and multiple dose, under fasting conditions (010-15-GLB)

Design
An open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover, single and multiple dose (steady state), oral bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 20-40 years. Subjects received a single dose (200 mg) of the test and reference mebeverine retard formulation at day 1 and thereafter at day 3, twice daily for days 3-5, one in the morning and one in the evening, with an interval of 12 hours between doses, and at day 6, once in the morning. The capsules were orally administered in solid form with 240 ml water under fasting conditions. The wash-out period was 6 days.

At day 1, blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 36 hours after administration of the products. At day 3 to 5 pre-dose (morning dose) and at day 6 at pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 10 and 12 h after the administration of the products.

The design of the single and multiple dose, crossover study to assess bioequivalence is considered adequate.

Results
One subject did not report for period II. Therefore, 49 subjects were eligible for pharmacokinetic analysis.

Single dose

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fasted conditions after a single dose.

Treatment N=49	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	18052.443 ± 5612.678	19012.023 ± 6010.118	2232.242 ± 490.755	2.750 ± 0.914	4.248 ± 1.644
Reference	18152.777 ± 6257.370	19108.576 ± 7101.608	2189.763 ± 576.664	2.500 ± 0.902	4.250 ± 3.15
***Ratio (90% CI)**	1.00 (0.94 – 1.08)	1.01 (0.94 – 1.08)	1.04 (0.96 – 1.10)	--	--
CV (%)	19.8	21.3	20.8	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mebeverine acid under fasted conditions after a single dose.

Treatment N=49	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	633.678 ± 319.694	654.607 ± 324.845	119.271 ± 49.551	2.500 ± 0.785	3.948 ± 2.110
Reference	116.400 ± 73.130	614.777 ± 351.282	116.400 ± 73.130	2.500 ± 0.933	3.281 ± 1.377
***Ratio (90% CI)**	1.05 (0.97 – 1.14)	1.06 (0.98 – 1.15)	1.08 (0.97 – 1.20)	--	--
CV (%)	24.2	24.2	32.4	--	--

$AUC_{0-\infty}$ 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*

Table 3. **Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine acid under fasted conditions after a single dose.**

Treatment N=49	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	1992.637 ± 604.074	2104.717 ± 663.913	263.330 ± 82.818	3.000 ± 1.010	4.325 ± 1.881
Reference	1989.528 ± 672.696	2102.934 ± 703.961	254.467 ± 94.680	3.250 ± 1.027	4.227 ± 1.604
***Ratio (90% CI)**	1.02 (0.95 – 1.09)	1.01 (0.94 – 1.09)	1.06 (0.98 – 1.13)	--	--
CV (%)	20.7	21.3	21.7	--	--

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

**ln-transformed values*

Table 4. **Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine alcohol under fasted conditions after a single dose.**

Treatment N=49	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	33.411 ± 15.427	35.500 ± 16.015	4.677 ± 2.159	4.500 ± 1.764	4.606 ±2.089
Reference	31.621 ± 16.330	33.825 ± 16.866	4.495 ± 2.408	4.500 ± 2.323	4.652 ± 2.100
***Ratio (90% CI)**	1.07 (0.98 – 1.17)	1.06 (0.98 – 1.15)	1.07 (0.97 – 1.19)	--	--
CV (%)	25.2	25.0	30.4	--	--

$AUC_{0-\infty}$ 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 (steady state)

Table 5. Pharmacokinetic parameters in steady-state of veratric acid (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ (ng/ml/h)	C_{max} (ng/ml)	C_τ (ng/ml)	PTF% (%)
Test	18214.765 ± 5701.271	2821.320 ± 856.296	853.735 ± 364.196	146.286 ± 45.748
Reference	19779.437 ± 7708.215	2863.490 ± 881.190	835.505 ± 464.982	137.26 ± 36.683
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	0.99 (0.94 – 1.05)	1.07 (0.97 – 1.17)	--
CV (%)	13.2	15.7	27.9	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_τ plasma concentration over the dosing interval
PTF% fluctuation index
CV coefficient of variation

**ln-transformed values*

Table 6. Pharmacokinetic parameters in steady-state of mebeverine acid (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ (ng/ml/h)	C_{max} (ng/ml)	C_τ (ng/ml)	PTF% (%)
Test	998.031 ± 449.673	199.049 ± 74.967	32.998 ± 24.158	221.267 ± 62.364
Reference	1038.382 ± 528.783	195.584 ± 82.611	30.354 ± 25.093	214.299 ± 72.361
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	1.03 (0.95 – 1.12)	1.17 (1.05 – 1.30)	--
CV (%)	15.0	23.8	32.8	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_τ plasma concentration over the dosing interval
PTF% fluctuation index
CV coefficient of variation

**ln-transformed values*

Table 7. Pharmacokinetic parameters in steady-state of desmethyl-mebeverine acid (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ (ng/ml/h)	C_{max} (ng/ml)	C_τ (ng/ml)	PTF% (%)
Test	1716.184 ± 450.048	267.711 ± 67.050	86.857 ± 31.848	149.220 ± 36.687
Reference	1857.244 ± 579.243	273.203 ± 75.050	77.868 ± 40.514	141.906 ± 39.332
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	0.99 (0.94 – 1.03)	1.16 (1.04 – 1.30)	--
CV (%)	12.6	13.3	33.3	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_τ plasma concentration over the dosing interval
PTF% fluctuation index
CV coefficient of variation

**ln-transformed values*

Table 8. Pharmacokinetic parameters in steady-state of desmethyl-mebeverine alcohol (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ (ng/ml/h)	C_{max} (ng/ml)	C_τ (ng/ml)	PTF% (%)
Test	24.429 ± 8.713	3.829 ± 1.351	1.294 ± 0.637	146.513 ± 42.389
Reference	26.145 ± 9.858	3.957 ± 1.597	1.207 ± 0.653	140.625 ± 44.3
***Ratio (90% CI)**	0.94 (0.89 – 0.99)	0.98 (0.90 – 1.06)	1.11 (0.99 – 1.25)	--
CV (%)	16.7	24.7	34.5	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_τ plasma concentration over the dosing interval
PTF% fluctuation index
CV coefficient of variation

**ln-transformed values*

Conclusion

Based on the submitted bioequivalence study under fasting conditions, after single dose, Mebeverine Aristo is considered bioequivalent with Colofac retard. Bioequivalence has been shown for veratric acid AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} within normal criteria.

In addition, at steady state, the Mebeverine Aristo is considered bioequivalent with Colofac retard. Bioequivalence has been shown for veratric acid $AUC_{0-\tau}$, $C_{max,ss}$ and $C\tau_{,ss}$ within normal criteria.

IV.2.2 Single dose, under fed conditions (202-11-EM)

Design

An open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-41 years. Subjects received a single dose (200 mg) of the test and reference mebeverine retard formulation. The capsules were orally administered in solid form with 240 ml water 30 minutes after the start of intake of a high fat high caloric breakfast. The wash-out period was 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 10, 12, 24 and 36 hours after administration of the products.

The design of the single dose, crossover study under fed conditions to assess bioequivalence is considered adequate.

Results

Two subjects were withdrawn due to protocol violation (not retaining posture and toilet restrictions), two subjects did not report for period II and one subject was withdrawn as he was found positive for drug abuse. Therefore, 35 subjects were eligible for pharmacokinetic analysis.

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fed conditions.

Treatment N=35	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	24408.554 ± 9075.959	30827.247 ± 9598.623	3685.141 ± 1462.316	4.5 ± 0.682	8.631 ± 4.819
Reference	24019.649 ± 8445.257	31353.338 ± 11795.830	3970.864 ± 1497.592	4.5 ± 0.609	8.577 ± 7191
***Ratio (90% CI)**	1.01 (0.94 – 1.09)	1.01 (0.92 – 1.10)	0.91 (0.83 – 1.00)	--	--
CV (%)	18.7	22.9	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*

Table 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mebeverine acid under fed conditions.

Treatment N=35	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	373.377 ± 387.636	966.487 ± 2514.106	105.037 ± 86.857	4.500 ± 0.565	0.351 ± 0.184
Reference	383.969 ± 349.439	511.999 ± 364.036	121.158 ± 103.190	4.500 ± 0.578	2.365 ± 1.762
***Ratio (90% CI)**	0.91 (0.78 – 1.07)	1.08 (0.85 – 1.37)	0.88 (0.77 – 1.01)	--	--
CV (%)	39.0	57.8	32.6	--	--

$AUC_{0-\infty}$ 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*

Table 11. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine acid under fed conditions.

Treatment N=35	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	4107.797 ± 872.341	4816.154 ± 925.072	751.878 ± 209.793	4.500 ± 0.726	7.241 ± 3.220
Reference	4320.705 ± 1096.578	4935.871 ± 1220.935	831.273 ± 259.544	4.500 ± 0.670	7.103 ± 3.527
***Ratio (90% CI)**	0.96 (0.90 – 1.01)	0.98 (0.93 – 1.04)	0.91 (0.80 – 1.04)	--	--
CV (%)	14.9	14.0	32.2	--	--

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

**ln-transformed values*

Table 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine alcohol under fed conditions.

Treatment N=35	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	48.668 ± 19.462	55.107 ± 18.693	9.371 ± 4.427	4.500 ± 0.661	5.764 ± 6.109
Reference	47.506 ± 19.477	52.304 ± 18.023	10.799 ± 5.304	4.500 ± 0.397	3.045 ± 1.068
***Ratio (90% CI)**	1.04 (0.97 – 1.11)	1.09 (1.03 – 1.16)	0.86 (0.78 – 0.96)	--	--
CV (%)	16.0	14.4	25.7	--	--

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

**ln-transformed values*

Conclusion
Based on the submitted bioequivalence study under fed conditions, Mebeverine Aristo is considered bioequivalent with Colofac retard. Bioequivalence has been shown for veratric acid AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} within normal criteria.

IV.2.3 Single dose, under fed conditions (014-16-GLB)

Design
An open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 21-40 years. Subjects received a single dose (200 mg) of the test and reference mebeverine retard formulation. The capsules were orally administered in solid form with 240 ml water 30 minutes after the start of intake of a high fat high caloric breakfast. The wash-out period was 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 36 hours after administration of the products.

The design of the additional single dose, crossover study to assess bioequivalence under fed conditions is considered adequate.

Results
One subject did not report for period II. Therefore, 31 subjects were eligible for pharmacokinetic analysis.

Table 13. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fed conditions.

Treatment N=31	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	17589 ± 4508.854	18386.315 ± 4477.396	2878.353 ± 894.263	4.500 ± 0.712	5.249 ± 8.036
Reference	17861.790 ± 4214.794	18461.984 ± 4259.609	284.665 ± 635.649	4.500 ± 0.583	3.736 ± 1.721
***Ratio (90% CI)**	0.98 (0.93 – 1.04)	0.99 (0.94 – 1.04)	0.99 (0.90 – 1.08)	--	--
CV (%)	12.87	11.65	21.09	--	--

$AUC_{0-\infty}$ 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*

Table 14. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mebeverine acid under fed conditions.

Treatment N=31	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	462.362 ± 199.169	473.972 ± 198.067	111.117 ± 49.403	4.500 ± 0.651	2.803 ± 1.381
Reference	427.400 ± 247.417	481.898 ± 247.167	108.417 ± 42.727	4.500 ± 0.582	2.064 ± 0.542
***Ratio (90% CI)**	1.00 (0.93 – 1.06)	1.00 (0.94 – 1.06)	0.99 (0.89 – 1.11)	--	--
CV (%)	14.96	14.32	25.82	--	--

$AUC_{0-\infty}$ 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*

Table 15. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine acid under fed conditions.

Treatment N=31	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5150.689 ± 1311.020	5259.772 ± 1353.242	989.333 ± 361.273	4.500 ± 0.887	3.695 ± 1.032
Reference	5151.865 ± 1223.168	5237.150 ± 1260.305	984.633 ± 286.815	4.500 ± 0.635	0.500 ± 0.258
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	1.00 (0.95 – 1.04)	0.98 (0.89 – 1.07)	--	--
CV (%)	10.80	10.97	21.04	--	--

$AUC_{0-\infty}$ 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*

Table 16. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl-mebeverine alcohol under fed conditions.

Treatment N=31	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	26.742 ± 10.314	28.250 ± 10.452	5.759 ± 2.232	4.500 ± 0.998	0.737 ± 0.355
Reference	27.111 ± 11.349	28.305 ± 11.452	5.820 ± 2.276	4.500 ± 0.802	2.967 ±0.970
***Ratio (90% CI)**	1.00 (0.93 – 1.07)	1.01 (0.94 – 1.08)	0.99 (0.89 – 1.12)	--	--
CV (%)	16.34	16.00	27.08	--	--

$AUC_{0-\infty}$ 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*

Conclusion
Based on the submitted bioequivalence study under fed conditions, Mebeverine Aristo is considered bioequivalent with Colofac retard. Bioequivalence has been shown for veratric acid AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} within normal criteria.

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $AUC_{0-\tau}$, $C_{max,ss}$ and $C\tau_{,ss}$ for veratric acid are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Mebeverine Aristo is considered bioequivalent with Colofac retard.

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 Mebeverine Aristo.

Table 17. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions including anaphylactic reactions • Skin reactions including urticarial, angioedema, face oedema, exanthema
Important potential risks	None
Missing information	• Use in pregnancy and breastfeeding women • Limited data on male or female infertility • Use in paediatric population

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 Colofac retard. No new clinical studies were conducted. The MAH demonstrated through 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 two 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

Mebeverine Aristo 200 mg modified release capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Colofac retard 200 mg capsule. Colofac retard 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 Mebeverine Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 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