CBG MEB

Public Assessment Report

Scientific discussion

Mebeverine HCl Aurobindo Retard 200 mg modified release capsules, hard

(mebeverine hydrochloride)

NL/H/3750/001/DC

Date: 18 September 2017

This module reflects the scientific discussion for the approval of Mebeverine HCl Aurobindo Retard 200 mg modified release capsules, hard. The procedure was finalised on 5 April 2017. 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
BP	British Pharmacopoeia
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
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 HCl Aurobindo Retard 200 mg modified release capsules, hard, from Aurobindo Pharma B.V.

The product is indicated for the symptomatic relief of irritable bowel syndrome in adults and children over 10 years.

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 Duspatal Retard 200 mg modified release capsules, hard (NL License RVG 11657) which has been registered in the Netherlands through a national procedure since 12 August 1987 by Abbott B.V. The innovator product is registered in several European countries under various trade names.

The concerned member states (CMS) involved in this procedure were Poland 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

Mebeverine HCl Aurobindo Retard is a hard gelatin, modified-release capsule, filled with white to off white spherical pellets. The product has a creamy white body and creamy white cap. Each capsule contains 200 mg mebeverine hydrochloride.

The capsules are packed in PVC/PVdC–Aluminium blisters.

The excipients are:
Capsule core - sugar spheres (sucrose, maize starch), povidone and hypromellose.
Sustained release coating – ethyl cellulose, macrogol and magnesium stearate.
Capsule shell – gelatin and titanium dioxide (E171).

II.2 Drug Substance

The active substance is mebeverine hydrochloride, an established active substance described in the British Pharmacopoeia (BP). Mebeverine hydrochloride is a white or almost white crystalline powder. The active substance is very soluble in water and in methylene chloride, 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. The substance is produced as a racemate. It has been demonstrated that the same polymorphic form (anhydrous crystalline 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
No class-1 solvents are used in the manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, 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 European Pharmacopoeia (Ph.Eur.) and BP. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance
Stability data on the active substance have been provided on three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The drug substance remains stable; there are no significant changes or unexpected results observed. Based on the data submitted, a retest period could be granted of 48 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 are explained. The choice of the manufacturing formula and process is also justified. The product is designed to have sustained release by selecting ethyl cellulose as a release retarding polymer in combination with magnesium stearate. The pharmaceutical development of the product has been adequately performed.

Two bioequivalence studies have been submitted. The drug product batches used in the bioequivalence study were manufactured according to the finalised composition and manufacturing process.

Manufacturing process
The manufacturing process is described in sufficient detail and is regarded as a non-standard process. It 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.

Control of excipients
All individual excipients comply with the Ph.Eur. The hard gelatin capsules are tested according to an in-house specification. 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, assay, related substances, residual solvents and microbial quality. The release and shelf-life limits are identical. 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 full scale 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 (two batches 36 months and one batch 12 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. 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 6 months for dissolution, individual unknown impurity and total impurities. The claimed shelf-life of 36 months and storage conditions ‘Do not store above 30°C’, ‘Do not refrigerate or freeze’ and ‘Store in the original package in order to protect from moisture’ are justified. The drug product is not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All excipients apart from gelatin are of non-animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mebeverine HCl Aurobindo Retard 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 HCl Aurobindo Retard 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 Duspatal Retard 200 mg 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 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Mebeverine HCl Aurobindo Retard 200 mg (Aurobindo Pharma B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Colofac retard 200 mg (Abbott Products GmbH, Austria). One bioequivalence study was carried out under fasting conditions, including a single dose treatment arm and a multiple dose treatment arm. The other bioequivalence study is a single dose fed study.

The choice of the reference product
The choice of the reference product, Colofac retard 200 mg modified release capsules, in the bioequivalence studies has been justified. Colofac retard has been registered in Austria by Abbott Products GmbH since 27 January 2000.

In the single dose fasting and steady state study and in the fed study a different biobatch was used, however both are representative for the commercial batch.

Bioequivalence study under fasting conditions

Design
A randomised, open-label, balanced, two-treatment, two-period, two-sequence, two-way crossover, single dose and multiple-dose, oral bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 20-40 years. Each subject received a single dose (200 mg) of one of the two mebeverine formulations 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 tablet was orally administered with 240 ml water under fasting conditions. The washout 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 hours after the administration of the products. Plasma samples were analysed for the pivotal analyte veratric acid, mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol.

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

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

For all analytes, repeat analysis were carried out for pharmacokinetic reasons. This may bias the outcome of the study. Therefore the original values were used to calculate the pharmacokinetics and statistics for the pivotal analyte veratric acid (table 5 and 10).

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

<u>Single treatment arm</u>

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fasted conditions after 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	18052.44 ± 5612.68	19012.02 ± 6010.12	2232.24 ± 490.76	2.75 (1.67 – 6.0)	4.25 ± 1.64
Reference	18152.78 ± 6257.37	19108.58 ± 7101.61	2189.76 ± 576.66	2.50 (1.33 – 4.5)	4.25 ± 3.15
***Ratio (90% CI)**	1.00 (0.94 – 1.07)	1.01 (0.94 – 1.08)	1.03 (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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mebeverine acid under fasted conditions after 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	633.68 ± 319.69	654.61 ± 324.85	119.27 ± 49.55	2.50 (1.33 – 4.5)	3.95 ± 2.11
Reference	614.78 ± 351.28	637.28 ± 376.81	116.40 ± 73.13	2.50 (1.33 – 4.5)	3.28 ± 1.38

$AUC_{0-\infty}$ 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

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl mebeverine acid under fasted conditions after 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	1992.64 ± 604.07	2104.72 ± 663.91	263.33 ± 82.82	3.00 (1.67 – 6.0)	4.33 ± 1.88
Reference	1989.53 ± 672.70	2102.93 ± 703.96	254.47 ± 94.68	3.25 (1.33 – 4.5)	4.23 ± 1.60

$AUC_{0-\infty}$ 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

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl mebeverine alcohol under fasted conditions after 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	33.41 ± 15.43	35.50 ± 16.02	4.68 ± 2.16	4.50 (1.67 – 10.0)	4.61 ± 2.09
Reference	31.62 ± 16.33	33.83 ± 16.87	4.50 ± 2.41	4.5 (1.67 – 10.0)	4.65 ± 2.10

$AUC_{0-\infty}$ 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

Table 5. Pharmacokinetic parameters based on original values (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fasted conditions.

Treatment N=49	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml
Test	17270.95	18165.37	2183.64
Reference	17255.71	18057.61	2119.02
***Ratio (90% CI)**	1.00 (0.94 – 1.07)	1.01 (0.94 – 1.08)	1.03 (0.96 – 1.10)
CV (%)	19.6	21.1	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
CV	coefficient of variation

**ln-transformed values*

After single dose, based on the pharmacokinetic parameters of the pivotal analyte veratric acid, the reference and test product are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25). For mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol bioequivalence could also be proven, supporting the results of veratric acid.

Steady state (multiple dose) arm

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

Treatment N=49	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_τ** ng/ml	**t_{max}** h	**PTF%** %
Test	18214.77 ± 5701.27	2821.32 ± 856.30	853.74 ± 364.20	3.00 ± 0.74	146.29 ± 45.75
Reference	19779.44 ± 7708.22	2742.64	835.51 ± 464.98	2.250 ± 1.03	137.21 ± 36.68
***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 de dosing interval
PTF%	fluctuation index
CV	coefficient of variation

**ln-transformed values*

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

Treatment N=49	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_τ** ng/ml	**tmax** h	**PTF%** %
Test	998.03 ± 449.67	199.05 ± 74.98	33.00 ± 24.16	3.00 ± 0.76	221.27 ± 62.36
Reference	1038.38 ± 528.78	195.58 ± 82.61	30.35 ± 25.01	2.250 ± 0.95	214.30 ± 72.36

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

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

Treatment N=49	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_τ** ng/ml	**t_{max}** h	**PTF%** %
Test	1716.18 ± 450.05	267.71 ± 67.05	86.86 ± 31.85	3.00 ± 0.93	149.22 ± 38.69
Reference	1857.24 ± 579.24	273.20 ± 75.05	77.87 ± 40.51	2.50 ± 1.18	141.91 ± 39.33

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

Table 9. Pharmacokinetic parameters of desmethyl mebeverine alcohol in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ ng/ml/h	C_{max} ng/ml	C_τ ng/ml	t_{max} h	PTF% %
Test	24.43 ± 8.71	3.83 ± 1.35	1.29 ± 0.64	3.50 ± 1.41	146.51 ± 42.39
Reference	26.15 ± 9.86	3.96 ± 1.60	1.21 ± 0.65	4.50 ± 2.12	140.63 ± 44.3

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

Table 10. Pharmacokinetic parameters of veratric acid in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=49	AUC_τ ng/ml/h	C_{max} ng/ml	C_τ ng/ml
Test	17483.45	2721.96	778.89
Reference	18594.27	2742.64	730.01
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	0.99 (0.94 – 1.05)	1.07 (0.97 – 1.17)
CV (%)	13.3	15.7	27.9

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

**ln-transformed values*

At steady state, based on the pharmacokinetic parameters of the pivotal analyte veratric acid, the reference and test products are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_τ, C_τ and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Bioequivalence study under fed conditions

Design
An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose crossover oral bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 19-41 years. Each subject received a single dose (200 mg) of one of the two mebeverine formulations. The tablet was orally administered with 240 ml water 30 minutes after the start of intake of a high fat high caloric breakfast. The washout period was seven 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. Plasma samples were analysed for the pivotal analyte veratric acid, mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol.

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

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Repeat analyses were carried out for pharmacokinetic reasons. This may bias the outcome of the study. For the pivotal analyte veratric acid no repeat analysis is carried out. The original values were be used for calculation of pharmacokinetics and statistics.

Results

Two subjects were withdrawn due to protocol violation, 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 11. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of veratric acid under fed conditions after single dose.

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	24408.55 ± 9075.96	30827.25 ± 9598.62	3685.14 ± 1462.32	4.50 ± 0.68	8.63 ± 4.82
Reference	24019.65 ± 8445.26	31353.34 ± 11795.83	3970.86 ± 1497.59	4.50 ± 0.61	8.58 ± 7.19
***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 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mebeverine acid under fed conditions after single dose.

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	373.38 ± 387.64	966.49 ± 2514.106	105.04 ± 86.86	4.50 ± 0.57	0.351 ± 0.18
Reference	383.969 ± 349.439	512.00 ± 364.04	121.16 ± 103.19	4.50 ± 0.58	2.365 ± 1.76
***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 13. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmethyl mebeverine acid under fed conditions after single dose.

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	4107.80 ± 872.34	4816.15 ± 925.07	751.88 ± 209.79	4.50 ± 0.73	7.24 ± 3.22
Reference	4320.71 ± 1096.58	4935.87 ± 1220.94	831.27 ± 259.54	4.50 ± 0.67	7.10 ± 3.53

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

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	48.67 ± 19.46	55.11 ± 18.69	9.37 ± 4.43	4.50 ± 0.66	5.76 ± 6.11
Reference	47.51 ± 19.48	52.30 ± 18.02	10.80 ± 5.30	4.50 ± 0.397	3.05 ± 1.07
***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*

Based on the pharmacokinetic parameters of veratric acid, the reference and test product are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

For mebeverine acid bioequivalence could not be proven for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, and for desmethyl-mebeverine alcohol bioequivalence could not be proven for C_{max}. However these parameters are not considered pivotal. In addition, considering the confidence intervals, it does not contradict the conclusion for veratric acid.

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. Based on the submitted bioequivalence studies Mebeverine HCl Aurobindo Retard 200 mg is considered bioequivalent with Colofac retard 200 mg.

The MEB has been assured that the bioequivalence studies have 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 HCl Aurobindo Retard.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity
Important potential risks	None
Missing information	• Use in pregnancy

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 Duspatal 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 has (PL) 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 HCl Aurobindo Retard 200 mg modified release capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Duspatal Retard 200 mg modified release capsules. Duspatal 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 HCl Aurobindo Retard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 April 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached