



# **Public Assessment Report**

## **UKPAR**

**Mebeverine 200 mg modified release capsules**

**(Mebeverine hydrochloride)**

**UK Licence Number: PL 35533/0095**

**Aspire Pharma Ltd.**

## LAY SUMMARY

### Mebeverine 200 mg modified release capsules (mebeverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Mebeverine 200 mg modified release capsules (PL 35533/0095). It explains how Mebeverine 200 mg modified release capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Mebeverine 200 mg modified release capsules (PL 35533/0095).

The product will be referred to as Mebeverine throughout the remainder of this public assessment report (PAR).

For practical information about using Mebeverine, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What is Mebeverine and what is it used for?**

Mebeverine is a 'generic medicine'. This means that Mebeverine is similar to a 'reference medicine' already authorised in the European Union (EU) called Colofac MR Modified release capsule (Mylan Products Ltd, UK).

This medicine is used to treat the symptoms of irritable bowel syndrome (IBS) which is a very common condition that causes spasm and pain in the gut or intestine.

#### **How does Mebeverine work?**

This medicine contains the active ingredient mebeverine hydrochloride which belongs to a group of medicines called antispasmodics.

The intestine is a long muscular tube which food passes down so it can be digested. If the intestine goes into spasm and squeezes too tightly, the patient gets pain. The way this medicine works is by relieving the spasm, pain and other symptoms of IBS.

The main symptoms of irritable bowel syndrome (IBS) include:

- stomach pain and spasm
- feeling bloated and having wind
- having diarrhoea (with or without constipation)
- small, hard, pellet-like or ribbon-like stools (faeces)

These symptoms may vary from person to person.

The patient should talk to their doctor or pharmacist if these symptoms do not improve after a while, if they develop new symptoms, or the patient is concerned about their symptoms.

#### **How is Mebeverine used?**

The pharmaceutical form of this medicine is a modified release capsule, and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

- Try to take the capsule 20 minutes before a meal - some people find their symptoms to be strongest after they have eaten.
- Swallow the capsule whole with a drink of water. Do not chew the capsule.

**Adults (including the elderly)**

- The recommended starting dose is one capsule twice a day.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Mebeverine is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Mebeverine have been shown in studies?**

Because Mebeverine is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine, Colofac MR Modified release capsule (Mylan Products Ltd, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Mebeverine?**

Because Mebeverine is a generic medicine and is bioequivalent to the reference medicine Colofac MR Modified release capsule (Mylan Products Ltd, UK), its benefits and possible side effects are taken as being the same as the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Mebeverine, see section 4 of the package leaflet available on the MHRA website.

**Why was Mebeverine approved?**

It was concluded that, in accordance with EU requirements, Mebeverine has been shown to have comparable quality and to be bioequivalent to Colofac MR Modified release capsule (Mylan Products Ltd, UK). Therefore, the MHRA decided that, as for Colofac MR Modified release capsule (Mylan Products Ltd, UK); the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Mebeverine?**

A risk management plan (RMP) has been developed to ensure that Mebeverine is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Mebeverine including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Mebeverine**

A Marketing Authorisation was granted in the UK on 14 July 2017.

The full PAR for Mebeverine follows this summary.

For more information about treatment with Mebeverine, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2017.

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## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Aspire Pharma Ltd a marketing authorisation for the medicinal product Mebeverine (PL 35533/0095) on 14 July 2017. The product is a prescription only medicine (POM) indicated for the symptomatic relief of IBS.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Colofac MR Modified release capsules which were originally authorised in the UK to Abbott Healthcare Products Limited (PL 00512/0155) on 14 August 1998 and underwent changes of ownership procedures, of which the most recent was to the current marketing authorisation holder Mylan Products Ltd (PL 46302/0023) on 28 July 2016. The reference product used for the bioequivalence studies is Colofac retard 200mg Kapseln (Abbott Products GmbH; marketing authorisation number 1-23472) which has been taken from the Austrian market. This is acceptable.

Mebeverine is a musculotropic antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract, without affecting normal gut motility. The exact mechanism of action is not known, but multiple mechanisms, such as a decrease in ion channel permeabilities, blockade of noradrenaline reuptake, a local anesthetic effect, changes in water absorption as well as weak anti-muscarinic and phosphodiesterase inhibitory effect might contribute to the local effect of mebeverine on the gastrointestinal tract. Systemic side-effects as seen with typical anti-cholinergics are absent.

Two bioequivalence studies (a single dose and multiple dose study conducted under fasting conditions and a single dose study conducted under fed conditions) were initially submitted to support this application. The single dose study conducted under fed conditions was found to be invalid and was not accepted and consequently will not be discussed further in this report. A further single dose fed study was submitted by the applicant which was found to be acceptable. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Mebeverine outweigh the risks and a Marketing Authorisation was granted.

## II QUALITY ASPECTS

### II.1 Introduction

Each modified release capsule contains 200 mg mebeverine hydrochloride as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

*Capsule core:*

Sugar spheres (sucrose, maize), povidone and hypromellose.

*SR Coating*

Ethyl cellulose N-45, macrogol 6000 and magnesium stearate.

*Capsule shell:*

Gelatin and titanium dioxide (E171).

The finished product is packaged in polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) blisters and is available in pack sizes of 10, 30 or 60 capsules. Not all pack sizes may be marketed.

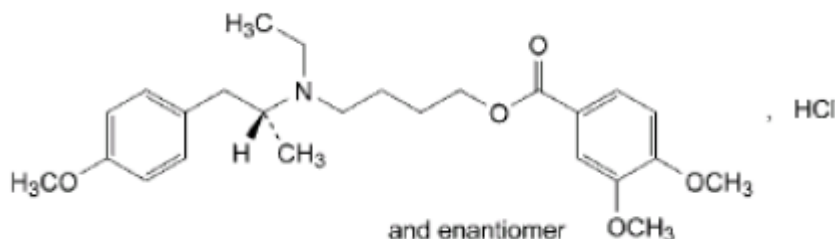
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

### II.2 Drug Substance

INN: Mebeverine hydrochloride

Chemical name: 4-[(1*RS*)-Ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]butyl 3,4-dimethoxybenzoate hydrochloride

Structure:



Molecular formula: C<sub>25</sub>H<sub>36</sub>ClNO<sub>5</sub>

Molecular weight: 466.0 g/mol

Description: White or almost white crystalline powder.

Solubility: Very soluble in water and in methylene chloride, freely soluble in ethanol (96%).

Mebeverine hydrochloride is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

### **II.3. Medicinal Product**

#### **Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious modified release capsules containing 200 mg mebeverine hydrochloride, per capsule, that are generic versions of the reference product Colofac MR Modified release capsule (Mylan Products Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the empty capsule shells which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of this product.

#### **Manufacture of the product**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

#### **Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

#### **Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with the storage conditions 'Store below 30°C. Store in the original package in order to protect from moisture.'

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of this application from a pharmaceutical viewpoint.

### III NON-CLINICAL ASPECTS

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of mebeverine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

#### III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Mebeverine 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.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

### IV CLINICAL ASPECTS

#### IV.1 Introduction

The clinical pharmacology of mebeverine hydrochloride is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of mebeverine hydrochloride.

Based on the data provided, Mebeverine (Aspire Pharma Ltd, UK) can be considered bioequivalent to Colofac retard 200mg Kapseln (Abbott Products GmbH).

#### IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence studies:

##### STUDY 1 (single dose and steady state)

**A randomised, open-label, balanced, two-treatment, two-period, two-sequence, two-way crossover, single dose and multiple-dose (steady state), oral bioequivalence study of the applicant's test product Mebeverine 200 mg modified release capsules (Aspire Pharma Ltd, UK) versus the reference product Colofac retard 200mg Kapseln (Abbott Products GmbH) in healthy, adult, human subjects under fasting conditions.**

Subjects were randomised to test or reference in period 1 and received the alternate randomisation in period 2. A single Mebeverine hydrochloride 200 mg SR capsule was administered on day 1 and a 36 hour pharmacokinetic profile taken over days 1 and 2. On day 3 onwards a multiple dosing phase of 7

doses at the 12 hour dosing interval commenced with pharmacokinetic sampling taken for 12 hours after the last dose.

For the single dose fasting phase, blood samples were collected for plasma levels before dosing and up to and including 36 hours post dose. For the multiple-dose (steady state) phase, blood samples were collected for plasma levels before dosing and up to and including 12 hours post dose. The washout period between the treatment phases was 7 days.

Mebeverine is almost completely metabolised after absorption and not detectable in plasma. Mebeverine is rapidly metabolised mainly by esterases, which split the ester bonds into veratric acid and mebeverine alcohol firstly and subsequently mebeverine alcohol oxidizes to form mebeverine acid. Mebeverine alcohol and mebeverine acid are further metabolised into desmethyl-mebeverine alcohol and desmethyl-mebeverine acid.

Plasma samples were analysed for veratric acid, mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol. The pharmacokinetic results are presented below:

**Table: Summary statistics for the pharmacokinetic parameters for veratric acid, desmethyl mebeverin alcohol, desmethyl mebeverin acid and mebeverin are presented below (geometric least squares means, ratio and 90% Confidence Intervals) administered under fasting conditions as a single dose and at steady state:**

#### Veratric acid (single dose)

Parameter		$C_{max}$ (ng/mL)	$AUC_{0-t}$ (ng.hr/mL)	$AUC_{0-inf}$ (ng.hr/mL)
Geometric LSM	T	2183.6436	17283.5549	18172.6191
	R	2119.0181	17216.1732	18014.4273
T/R Ratio (%):		103.05%	100.39%	100.88%
90% Confidence Interval:		96.11% to 110.49%	93.93% to 107.30%	93.93% to 108.34%
BE acceptance criteria		80% - 125%	80% - 125%	80% - 125%

#### Veratric acid (multiple dose-steady state)

Parameter		$C_{max, ss}$ (ng/mL)	$C_{\tau, ss}$ (ng/mL)	$AUC_{(0-\tau) ss}$ (ng.hr/mL)
Geometric LSM	T	2721.9629	778.8872	17476.6246
	R	2742.6406	730.0100	18638.0954
T/R Ratio (%):		99.25%	106.70%	93.77%
90% Confidence Interval:		94.13% to 104.64%	97.25% to 117.06%	89.69% to 98.03%
BE acceptance criteria		80% - 125%	80% - 125%	80% - 125%

**Desmethyl Mebeverin Alcohol**

PK Parameter	Geometric LSM		Ratio T/R	90%CI Lower	90%CI Upper	Power	ISCV	BE
	R	T						
<b>Single Dose</b>								
$C_{max}$	3.9577	4.2487	107.35%	97.06%	118.73%	97.6%	30.4%	YES
$AUC_t$	28.3889	30.4093	107.12%	98.49%	116.50%	99.6%	25.2%	YES
$AUC_i$	30.6045	32.4704	106.10%	97.60%	115.33%	99.6%	25.0%	YES
<b>Multiple Dose - Steady State</b>								
$C_{max}$	3.6347	3.5559	97.83%	90.09%	106.24%	99.7%	24.7%	YES
$AUC_{tau}$	24.3850	22.8898	93.87%	88.73%	99.31%	100.0%	16.7%	YES
$C_{tau}$	1.0338	1.1491	111.15%	99.22%	124.53%	94.4%	34.5%	YES

**Desmethyl Mebeverin Acid**

PK Parameter	Geometric LSM		Ratio T/R	90%CI Lower	90%CI Upper	Power	ISCV	BE
	R	T						
<b>Single Dose</b>								
$C_{max}$	239.0834	252.2354	105.50%	98.10%	113.47%	99.9%	21.7%	YES
$AUC_t$	1869.8123	1901.7993	101.71%	94.89%	109.02%	100.0%	20.7%	YES
$AUC_i$	1981.1496	2005.6071	101.23%	94.27%	108.71%	100.0%	21.3%	YES
<b>Multiple Dose - Steady State</b>								
$C_{max}$	262.6552	259.5820	98.83%	94.49%	103.37%	100.0%	13.3%	YES
$AUC_{tau}$	1771.0137	1658.7618	93.66%	89.77%	97.72%	100.0%	12.6%	YES
$C_{tau}$	69.3250	80.4421	116.04%	103.84%	129.66%	95.2%	33.3%	NO

**Mebeverin Acid**

PK Parameter	Geometric LSM		Ratio T/R	90%CI Lower	90%CI Upper	Power	ISCV	BE
	R	T						
<b>Single Dose</b>								
$C_{max}$	101.8859	110.1538	108.11%	97.13%	120.34%	96.2%	32.4%	YES
$AUC_t$	535.3770	563.5806	105.27%	97.10%	114.12%	99.8%	24.2%	YES
$AUC_i$	553.3737	585.1295	105.74%	97.52%	114.65%	99.8%	24.2%	YES
<b>Multiple Dose - Steady State</b>								
$C_{max}$	177.7636	183.7560	103.37%	95.47%	111.92%	99.8%	23.8%	YES
$AUC_{tau}$	910.0556	899.3456	98.82%	93.95%	103.95%	100.0%	15.0%	YES
$C_{tau}$	21.7577	25.3585	116.55%	104.59%	129.87%	95.9%	32.8%	NO

**Study Conclusion**

Adequate justification for the choice of veratric acid as the pivotal metabolite for bioequivalence assessment has been submitted.

For desmethyl mebeverine alcohol, desmethyl mebeverine acid and mebeverine acid, bioequivalence could be proven after single dose. At steady state, bioequivalence could be proven for desmethyl mebeverine alcohol for  $C_{max}$ ,  $AUC_{tau}$  and  $C_{tau}$ , desmethyl mebeverine acid  $C_{max}$  and  $AUC_{tau}$  and mebeverine acid  $C_{max}$  and  $AUC_{tau}$ .

The 90% confidence intervals of the test/reference ratio for AUC and  $C_{max}$  values for veratric acid, desmethyl mebeverine alcohol, desmethyl mebeverine acid and mebeverine acid (administered as a single dose and under steady state conditions) lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Colofac retard 200mg Kapseln (Abbott Products GmbH).

## STUDY 2

**A randomised, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral bioequivalence study of the applicant's test product Mebeverine 200 mg modified release capsules (Aspire Pharma Ltd, UK) versus the reference product Colofac retard 200mg Kapseln (Abbott Products GmbH) in healthy, adult, human subjects under fed conditions.**

Subjects were administered a single dose (1 x 200 mg modified release capsule) of the test or reference product with 240 ml water 30 minutes after start of intake of a high fat high caloric breakfast.

Blood samples were collected for plasma levels before dosing and upto and including 36 hours post dose. The washout period between the treatment phases was 7 days. Plasma samples were analysed for veratric acid, mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol. The pharmacokinetic results are presented below:

**Summary statistics for the pharmacokinetic parameters for veratric acid, desmethyl mebeverin alcohol, desmethyl mebeverin acid and mebeverin are presented below (geometric least squares means, ratio and 90% Confidence Intervals) administered as a single dose under fed conditions:**

PK Parameter	Geometric LSM		Ratio T/R	90%CI Lower	90%CI Upper	Power	ISCV	BE
	R	T						
<b>Veratric acid</b>								
$C_{max}$	2785.858	2748.067	98.64%	90.14%	107.94%	99.10%	21.09%	YES
AUC <sub>0-t</sub>	17371.928	17019.872	97.97%	92.70%	103.55%	100.00%	12.87%	YES
AUC <sub>0-inf</sub>	17988.020	17835.161	99.15%	94.30%	104.25%	100.00%	11.65%	YES
<b>Mebeverine Acid (supportive information)</b>								
$C_{max}$	101.441	100.817	99.38%	89.06%	110.91%	95.53%	25.82%	
AUC <sub>0-t</sub>	428.649	426.712	99.55%	93.35%	106.15%	99.99%	14.96%	
AUC <sub>0-6</sub>	270.456	272.688	100.83%	92.75%	109.60%	99.59%	19.52%	
AUC <sub>6-36</sub>	155.329	149.248	96.09%	86.43%	106.82%	96.49%	24.91%	
AUC <sub>0-inf</sub>	439.134	439.737	100.14%	94.16%	106.49%	99.99%	14.32%	
<b>Desmethyl Mebeverine acid (supportive information)</b>								
$C_{max}$	948.421	926.503	97.69%	89.29%	106.87%	99.13%	21.04%	
AUC <sub>0-t</sub>	5011.634	4968.617	99.14%	94.64%	103.86%	100.00%	10.80%	
AUC <sub>0-inf</sub>	5092.295	5071.965	99.60%	95.01%	104.42%	100.00%	10.97%	
<b>Desmethyl Mebeverine alcohol (supportive information)</b>								
$C_{max}$	5.346	5.316	99.44%	88.65%	111.54%	94.00%	27.08%	
AUC <sub>0-t</sub>	25.262	25.239	99.91%	93.15%	107.17%	99.96%	16.34%	
AUC <sub>0-inf</sub>	26.488	26.765	101.04%	94.34%	108.22%	99.97%	16.00%	

90% confidence intervals for Ln-transformed of  $C_{max}$ , AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> of Veratric acid are within the acceptable bioequivalence criteria.

## Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and  $C_{max}$  values for veratric acid, desmethyl mebeverine alcohol, desmethyl mebeverine acid and mebeverine acid (administered as a single dose under fasting conditions) lie within the acceptable limits of 80.00% to 125.00%, in line with

the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Colofac retard 200mg Kapseln (Abbott Products GmbH).

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none are required.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> <li>Hypersensitivity reactions including anaphylactic reactions</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>None</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>Use in pregnancy and breastfeeding women</li> <li>Use in paediatric population</li> </ul>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

### IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

## V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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.

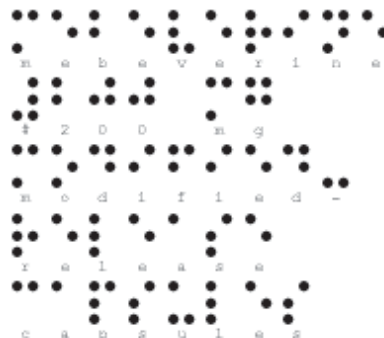
## VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mebeverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:





## Annex 1

### Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome