Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Mebeverine Hydrochloride 135mg film-coated tablets

(mebeverine hydrochloride)

UK Licence Numbers: PL 35533/0125

Aspire Pharma Ltd.

LAY SUMMARY

Mebeverine Hydrochloride 135mg film-coated tablets
(mebeverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Mebeverine Hydrochloride 135mg film-coated tablets (PL 35533/0125). It explains how Mebeverine Hydrochloride 135mg film-coated tablets were assessed and why authorisation was recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Mebeverine Hydrochloride 135mg film-coated tablets.

The product will be referred to as Mebeverine Hydrochloride tablets throughout the remainder of this PAR.

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

What are Mebeverine Hydrochloride tablets and what are they used for?
Mebeverine Hydrochloride tablets are a 'generic medicine'. This means that Mebeverine Hydrochloride tablets are similar to a 'reference medicine' already authorised in the EU called Colofac Tablets 135 mg (Mylan Products Ltd, UK).

This medicine is used to treat symptoms of irritable bowel syndrome (IBS) and similar conditions such as chronic irritable colon, spastic constipation, mucous colitis and spastic colitis.

IBS is a very common condition which causes spasm and pain in the gut and intestine.

The main symptoms of 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.

How do Mebeverine Hydrochloride tablets work?
This medicine contains the active ingredient mebeverine hydrochloride which belongs to a group of medicines called antispasmodics. Mebeverine helps to relax the muscles of the gastro-intestinal tract (gut).

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.

How are Mebeverine Hydrochloride tablets used?
The pharmaceutical form of this medicine is a film-coated tablet 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 unsure.

The number of tablets the patient takes can be lowered if their symptoms improve.

- **Do not take more than 3 tablets per day.**
- Try to take the tablet twenty minutes before a meal; some people find their symptoms are strongest after they have eaten.
- Swallow the tablet whole with water. Do not chew the tablet.

Adults (including the elderly)

- Take 1 tablet 3 times 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 Hydrochloride tablets are used, refer to the package leaflet and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Mebeverine Hydrochloride tablets can only be obtained with a prescription.

What benefits of Mebeverine Hydrochloride tablets have been shown in studies?
As Mebeverine Hydrochloride tablets are a generic medicine, studies have been limited to tests to determine that they are bioequivalent to the reference medicine Colofac Tablets 135 mg (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 Hydrochloride tablets?
Mebeverine Hydrochloride tablets are a generic medicine and are bioequivalent to the reference medicine Colofac Tablets 135 mg (Mylan Products Ltd, UK) so the benefits and possible side effects are taken as being the same as for the reference medicine.

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

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

Why were Mebeverine Hydrochloride tablets approved?
It was concluded that, in accordance with EU requirements, Mebeverine Hydrochloride tablets have been shown to have comparable quality and to be bioequivalent to Colofac Tablets 135 mg (Mylan Products Ltd, UK). Therefore, the MHRA decided that, as for Colofac Tablets 135 mg (Mylan Products Ltd, UK), the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Mebeverine Hydrochloride tablets?
A risk management plan (RMP) has been developed to ensure that Mebeverine Hydrochloride tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for Mebeverine Hydrochloride tablets 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 Hydrochloride tablets
A Marketing Authorisations was granted in the UK on 14 June 2018.

The full PAR for Mebeverine Hydrochloride tablets follows this summary.

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

This summary was last updated in July 2018.

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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 Hydrochloride tablets (PL 35533/0125) on 14 June 2018.

Mebeverine Hydrochloride tablets are a prescription only medicine (POM) indicated for the symptomatic treatment of irritable bowel syndrome and other conditions usually included in this grouping, such as: chronic irritable colon, spastic constipation, mucous colitis, spastic colitis. Mebeverine Hydrochloride tablets are effectively used to treat the symptoms of these conditions, such as: colicky abdominal pain and cramps, persistent non-specific diarrhoea (with or without alternating constipation) and flatulence.

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 Tablets 135 mg (PL 46302/0021) which was first authorised to Abbott Healthcare Products Limited on 14 March 1978 (PL 00512/0044) and underwent several changes of ownership procedures of which the most recent was to the current marketing authorisation holder (MAH) Mylan Products Ltd on 04 August 2016 (PL 46302/0021).

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 antimuscarinergic 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.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was 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 Hydrochloride tablets outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 135mg of mebeverine hydrochloride as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Core tablet

Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate type A, povidone, magnesium stearate and talc

Film-coating

Opadry white (consisting of hypromellose (E464), titanium dioxide (E171), polyethylene glycol/macrogol and talc)

The finished product is packaged in:

- polyvinylchloride/polyvinylidene chloride (PVC/PVdC)-aluminium blisters in pack sizes of 10, 15, 84 or 100 film-coated tablets.

Not all pack sizes may be marketed.

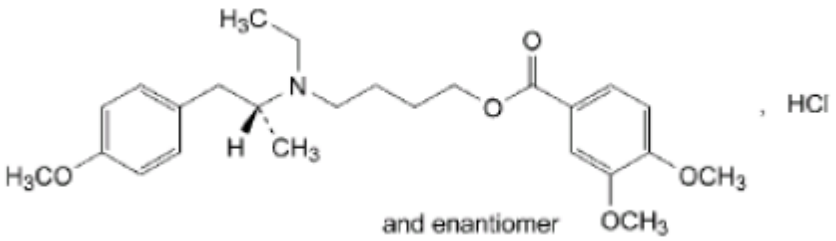
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

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: $C_{25}H_{35}NO_5$,HCl

Molecular weight: 466.0

Appearance: A white or almost white, crystalline powder.

Solubility: Very soluble in water; freely soluble in ethanol (96%); practically insoluble in ether.

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, film-coated tablets containing 135 mg, mebeverine hydrochloride per tablet, that are generic versions of the reference product Colofac Tablets 135 mg (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 film-coating which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

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 release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which 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 30 months for the unopened blisters with no special storage conditions.

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 Hydrochloride tablets are 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 study 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 Hydrochloride tablets can be considered bioequivalent to Colofac tablets 135mg (Mylan Products Limited, UK).

IV.2 Pharmacokinetics

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

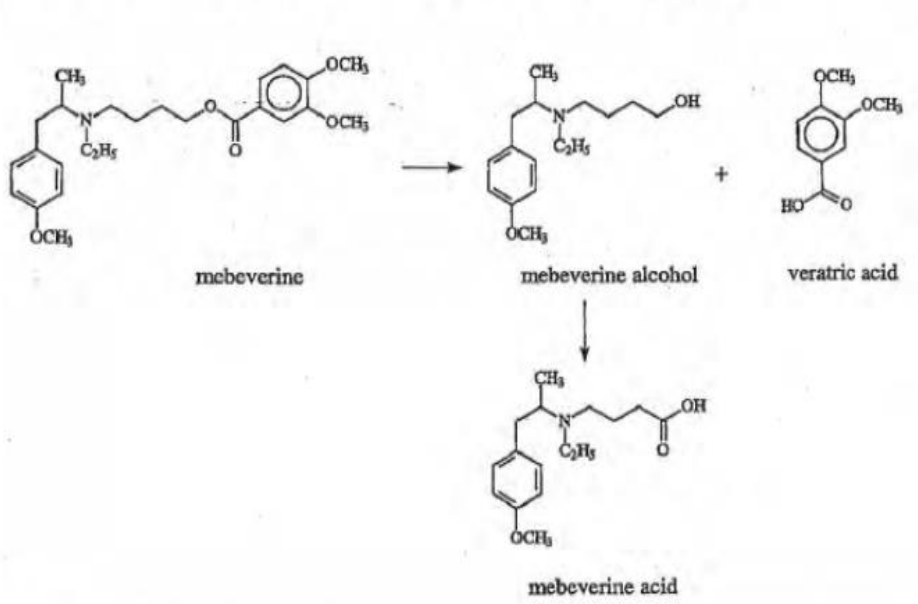
STUDY

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover, oral bioequivalence study of the applicant's test product Mebeverine Hydrochloride 135mg film-coated tablets (Aspire Pharma Ltd, UK) versus the reference product Colofac tablets 135mg (Mylan Products Limited, UK) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x 135 mg film-coated tablet) of the test or reference product.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 9 days. The pharmacokinetic results are presented below on page 11 of this report.

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 (see figure below).



Mebeverine alcohol and mebeverine acid are further metabolised into desmethyl mebeverine alcohol and desmethyl-mebeverine acid (DMAC).

Since mebeverine is almost completely metabolised after absorption and not detectable in plasma, mebeverine metabolites are used as surrogate measures of the parent molecule in bioequivalence (BE) studies. Since mebeverine acid and desmethyl mebeverine acid are the result of a metabolic step from the first metabolite formed, this is considered less sensitive to detect differences between formulation based upon pharmacokinetics. Therefore, veratric acid can be considered the pivotal analyte on which to base a decision on bioequivalence, with the other analytes being supportive.

The applicant has analysed the content of veratric acid, mebeverine acid, desmethylmebeverine acid (DMAC) and desmethyl-mebeverine alcohol. The results are presented below:

Results

Table: Summary of pharmacokinetic data for veratric acid (geometric mean ratio, and 90% Confidence Interval):

Parameter		Ln C_{max}	Ln AUC_{0-t}	Ln AUC_{0-inf}
Geometric LSM	T	6095.333	16249.540	16596.267
	R	6690.813	16332.071	16692.786
T/R Ratio (%):		91.10%	99.49%	99.42%
90% Confidence Interval:		85.14%-97.48%	97.04-102.01%	96.95%-101.1%
BE acceptance criteria		80%-125%	80%-125%	80%-125%
p-values (ANOVA):				
Sequence		0.2702	0.5207	0.4704
Subject (Sequence)		0.0002	<.0001	<.0001
Period		0.7507	0.0386	0.0329
Treatment		0.0259	0.7338	0.6992
Intra-subject Variability (%):		16.83%	6.18%	6.23%
Power (%)		99.98%	100.00%	100.00%

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from zero to infinity hours
C_{max} maximum plasma concentration

Table: Summary of pharmacokinetic data for mebeverine acid (geometric mean ratio, and 90% Confidence Interval):

Parameter		Ln C_{max}	Ln AUC_{0-t}	Ln AUC_{0-inf}
Geometric LSM	T	348.913	754.837	761.942
	R	367.339	744.551	752.739
T/R Ratio (%):		94.98%	101.38%	101.22%
90% Confidence Interval:		85.82%-105.12%	96.44%-106.58%	96.32%-106.37%
BE acceptance criteria		80%-125%	80%-125%	80%-125%
p-values (ANOVA):				
Sequence		0.0025	<.0001	<.0001
Subject (Sequence)		<.0001	<.0001	<.0001
Period		0.5184	0.8348	0.7752
Treatment		0.3967	0.6452	0.6813
Intra-subject Variability (%):		25.46%	12.39%	12.31%
Power (%)		97.48%	100.00%	100.00%

Table: Summary of pharmacokinetic data for desmethyl mebeverine acid (DMAC) (geometric mean ratio, and 90% Confidence Interval):

Parameter		Ln C_{max}	Ln AUC_{0-t}	Ln AUC_{0-inf}
Geometric LSM	T	1558.225	3764.509	3823.105
	R	1640.389	3719.035	3778.519
T/R Ratio (%):		94.99%	101.22%	101.18%
90% Confidence Interval:		88.64%-101.79%	98.23%-104.31%	98.21%-104.24%
BE acceptance criteria		80%-125%	80%-125%	80%-125%
p-values (ANOVA):				
Sequence		0.9297	0.0004	0.0004
Subject (Sequence)		<.0001	<.0001	<.0001
Period		0.4081	0.8111	0.8668
Treatment		0.2175	0.4986	0.5105
Intra-subject Variability (%):		17.22%	7.44%	7.38%
Power (%)		99.97%	100.00%	100.00%

Table: Summary of pharmacokinetic data for desmethyl mebeverine alcohol (geometric mean ratio, and 90% Confidence Interval):

Parameter		Ln C_{max}	Ln AUC_{0-t}	Ln AUC_{0-inf}
Geometric LSM	T	8.135	14.559	15.320
	R	8.988	15.606	16.251
T/R Ratio (%):		90.51%	93.29%	94.27%
90% Confidence Interval:		80.60%-101.63%	87.46%-99.52%	88.51%-100.41%
BE acceptance criteria		80%-125%	80%-125%	80%-125%
p-values (ANOVA):				
Sequence		0.5344	0.2427	0.3438
Subject (Sequence)		<.0001	<.0001	<.0001
Period		0.1117	0.1035	0.0900
Treatment		0.1549	0.0779	0.1231
Intra-subject Variability (%):		29.24%	16.06%	15.68%
Power (%)		93.65%	99.99%	99.99%

Study conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for the pivotal analyte veratric acid and metabolites mebeverine acid, desmethyl mebeverine acid and desmethyl mebeverine alcohol 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 Mebeverine Hydrochloride 135mg film-coated tablets (Aspire Pharma Ltd, UK) is bioequivalent to the reference product Colofac tablets 135mg (Mylan Products Limited, UK).

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.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Mebeverine 200mg modified-release capsules (PL35533/0095) The bridging report submitted by the applicant is acceptable.

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:

2D barcode and human-readable data will be included on this panel when implemented

Mebeverine hydrochloride
135mg
film-coated tablets

Contains lactose. See leaflet for further information.
Read the package leaflet before use.
Oral use.
Keep out of the sight and reach of children.
Take as directed by your doctor.

5 060209 731940

Pharmacy labels to state lactose if appropriate

MA Holder:
Aspire Pharma Ltd
Unit 4, Rocherbrook Court
Bedford Road, Petersfield
Hampshire, GU32 3QG, UK

POM
PL 35533/0125
1010408-C17

100 film-coated tablets

ASPIRE Pharma

Mebeverine hydrochloride
135mg
film-coated tablets

100 film-coated tablets

Mebeverine hydrochloride
135mg
film-coated tablets

100 film-coated tablets

Mebeverine hydrochloride
135mg
film-coated tablets

Each film-coated tablet contains
135mg of mebeverine hydrochloride.

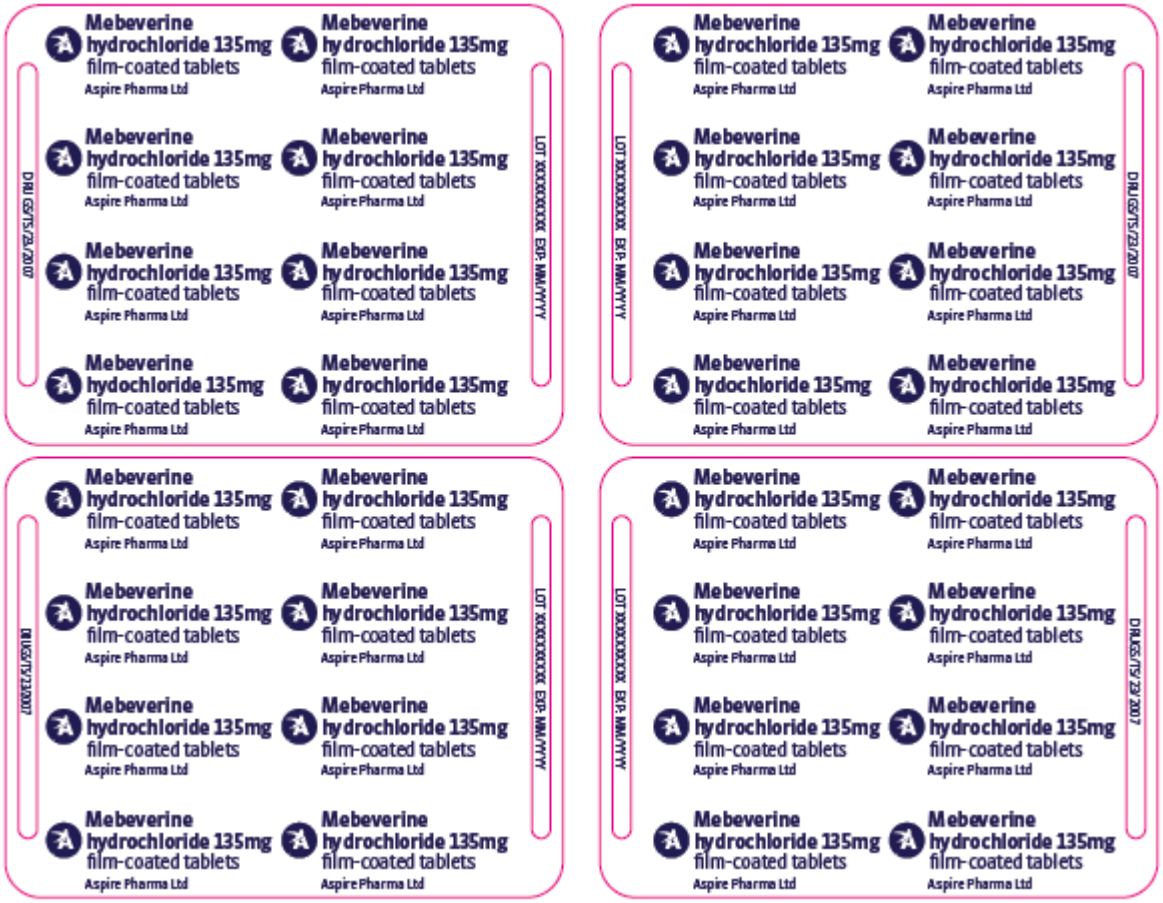
100 film-coated tablets

Mebeverine hydrochloride
135mg
film-coated tablets

100 film-coated tablets

DRUGS/TS/23/2007

mebeverine hydrochloride 135mg film-coated tablets



Braille Reads

Mebeverine

Hydrochloride

#135 mg

Film-coated

Tablets

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