Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mebeverine hydrochloride 135 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 135 mg of Mebeverine hydrochloride.

Excipients with known effect: Each tablet contains 97 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White colored, circular biconvex shaped, film-coated tablets, plain on both the sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in the management of irritable bowel syndrome, (particularly gastrointestinal spasm).

4.2 Posology and method of administration

Posology
The film-coated tablets should be swallowed with a sufficient amount of water (at least 100 ml water). They should not be chewed because of the unpleasant taste.

Duration of use is not limited.

If one or more doses are missed, the patient should continue with the next dose as prescribed; the missed dose(s) should not be taken in addition to the regular dose.

Adults (including the elderly):
One tablet three times a day, preferably 20 minutes before meals. After a period of several weeks, when the desired effect has been obtained, the dosage may be gradually reduced.

Warning: Do not exceed the stated dose.

Paediatric Population:
Mebeverine coated tablets are not recommended for use in children and adolescents below 18, due to insufficient data on safety and efficacy.

Special Population:
No posology studies in elderly, renal and/or hepatic impaired patients have been performed. No specific risk for elderly, renal and/or hepatic impaired patients could be identified from available post-marketing data. No dosage adjustment is deemed necessary in elderly, renal and/or hepatic impaired patients.

Method of administration
For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Since Mebeverine coated tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed, except with alcohol. *In vitro* and *in vivo* studies in animals have demonstrated the absence of any interaction between mebeverine hydrochloride and ethanol.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amounts of data from the use of mebeverine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Mebeverine coated tablets is not recommended during pregnancy.

Breastfeeding
It is unknown whether mebeverine or its metabolites are excreted in human milk. The excretion of mebeverine in milk has not been studied in animals. Mebeverine coated tablets should not be used during breast-feeding.

Fertility
There are no clinical data on male or female fertility; however, animal studies do not indicate harmful effects of mebeverine (see section 5.3).

4.7 Effects on ability to drive and use machines

No known studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic and pharmacokinetic profile as well as postmarketing experience does not indicate any harmful effect of mebeverine on the ability to drive or to use machines.

4.8 Undesirable effects

The following adverse reactions have been reported spontaneously during postmarketing use. A precise frequency cannot be estimated from available data.

Allergic reactions mainly but not exclusively limited to the skin have been observed.

Immune system disorders:
Hypersensitivity (anaphylactic reactions).

Skin and subcutaneous tissue disorders:
Urticaria, angioedema, face oedema, exanthema.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Theoretically CNS excitability may occur in cases of overdose. In cases where mebeverine was taken in overdose, symptoms were either absent or mild and usually rapidly reversible. Observed symptoms of overdose were of a neurological and cardiovascular nature.

No specific antidote is known and symptomatic treatment is recommended.

Gastric lavage should only be considered in case of multiple intoxication or if discovered within about one hour. Absorption reducing measures are not necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Synthetic anticholinergics, esters with tertiary amino group, ATC Code: A03A A04.

Mechanism of action
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.

Clinical efficacy and safety
All formulations of mebeverine were generally safe and well tolerated in the recommended dose regimen.

Paediatric population
The safety and efficacy of the product has only been evaluated in adults.

5.2 Pharmacokinetic properties

Absorption:
Mebeverine is rapidly and completely absorbed after oral administration of tablets.

Distribution:
No significant accumulation occurs after multiple doses.

Biotransformation:
Mebeverine hydrochloride is mainly metabolised by esterases, which split the ester bonds into veratric acid and mebeverine alcohol firstly.
The main metabolite in plasma is DMAC (demethylated carboxylic acid).
The steady state elimination half-life of DMAC is 2.45 h. During multiple dosing C_{max} of DMAC for the coated tablets with 135 mg is 1670ng/ml and t_{max} is 1 h.

Elimination:
Mebeverine is not excreted as such, but metabolised completely; the metabolites are excreted nearly completely. Veratric acid is excreted into the urine; mebeverine alcohol is also excreted into the urine, partly as the corresponding carboxylic acid (MAC) and partly as the demethylated carboxylic acid (DMAC).

Paediatric population:
The safety and efficacy of the product has only been evaluated in adults.

5.3 Preclinical safety data

Effects in repeat-dose toxicity studies, after oral and parenteral doses, were indicative of central nervous involvement with behavioural excitation, mainly tremor and convulsions. In the dog, the most sensitive species, these effects were seen at oral doses equivalent to 3 times the maximum recommended clinical dose of 400mg/day based on body surface area (mg/m^2) comparisons.

The reproductive toxicity of mebeverine was not sufficiently investigated in animal studies.

There was no indication of teratogenic potential in rats and rabbits. However, embryotoxic effects (reduction in litter size, increased incidence of resorption) were noticed in rats at doses equivalent to twice the maximum daily clinical dose. This effect was not observed in rabbits. No effects on male or female fertility were noted in rats at doses equivalent to the maximum clinical dose.

In conventional in vitro and in vivo genotoxicity tests mebeverine was devoid of genotoxic effects. No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (Type A)
Povidone
Talc
Magnesium stearate

Film-coating
Hypromellose (HPMC E3)
Macrogols (PEG 400)
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 36 months.

HDPE Bottle:
Unopened - 30 months
After opening - 90 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/PVC/PVdC blister pack: 12, 15, 18, 20, 21, 28, 30, 56, 60, 84, 90 and 100 tablets.

HDPE Bottle: 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER

PA22871/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd November 2019
Date of last renewal: 21st November 2024

10 DATE OF REVISION OF THE TEXT

April 2024