SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aurobeverine MR 200 mg modified-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg mebeverine hydrochloride

Excipient with known effect:
Each capsule contains up to 23.81 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Creamy white body and creamy white cap, hard gelatin capsule (approximately 9.8 mm x 6.9 mm) filled with white to off white spherical pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic relief of irritable bowel syndrome in adults.

4.2 Posology and method of administration

Posology

Adults:
One capsule of 200 mg twice daily; one in the morning and one in the evening.

There are no safety risks for continued use up to a period of 1 year. However, once the desired effect is achieved after several weeks, the dose can be gradually reduced.

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.

Paediatric Population
Aurobeverine MR is not recommended for use in children and adolescents below 18, due to insufficient data on safety and efficacy.
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.

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

Aurobeverine MR should be swallowed with a sufficient amount of water (at least 100 ml water). They should not be chewed because the coating is intended to ensure a controlled release (see section 5.2).

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltese insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of mebeverine are known.

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 is not recommended during pregnancy.

Breast-feeding

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 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 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 do 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple Store.

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 and pharmacodynamics effects

Mebeverine is a musculotropic antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract, relieving spasm 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-

muscarinergic and phosphodiesterase inhibitory effect might contribute to the local effect of mebeverine on the gastrointestinal tract. Since the autonomic nervous system is not involved in this mechanism of action, typical systemic anticholinergic side-effects are absent.

Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

Absorption
Mebeverine is rapidly and completely absorbed after oral administration of tablets. The modified release formulation permits a twice daily dosing scheme.

Distribution
No significant accumulation occurs after multiple doses.

Biotransformation
Mebeverine hydrochloride is mainly metabolised by esterases, initially splitting the ester bonds into veratric acid and mebeverine alcohol. The main metabolite in plasma is DMAC (Demethylated carboxylic acid). The steady state elimination half-life of DMAC is 5.77h. During multiple dosing (200 mg b.i.d.) the Cmax of DMAC is 804 ng/ml and tmax is about 3 hrs. The relative bioavailability of the modified release capsule appears to be optimal with a mean ratio of 97%.

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 efficacy and safety 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 tremors and convulsions. In dogs, the most sensitive species, these effects were seen at oral doses equivalent to 3 times the maximum recommended clinical dose of 400 mg/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

Capsule core:

Sugar spheres (sucrose, maize starch)

Povidone

Hypromellose

SR coating:

Ethylcellulose

Macrogol

Magnesium stearate

Capsule shell:

Gelatin

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

For blister packs: 36 months

For HDPE container packs: 36 months

In use shelf life for HDPE container packs:

3 months

6.4 Special precautions for storage

Blister Pack:

Do not store above 30°C. Do not refrigerate or freeze. Store in the original package in order to protect from moisture.

HDPE container pack:

Store below 25°C. Store in the original container in order to protect from light and moisture.

6.5 Nature and contents of container

Blister pack: PVC/PVdC – Aluminium blisters in cartons.

Pack sizes of blister: 20, 30, 50, 60, 90 and 100 capsules.

HDPE container pack: HDPE bottles fitted with round white screw type continuous thread cap.

Pack sizes of HDPE container: 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

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