Summary of Product Characteristic
Mebeverine Hydrochloride

1 NAME OF THE MEDICINAL PRODUCT

Duspatalin 200 mg, prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Duspatalin200mg, prolonged- release capsules, hard:
One prolonged-release capsule, hard, contains 200 mg mebeverine hydrochloride. For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Opaque white, hard gelatine capsule of size no. 1, with standard imprint 245.

4.1 Therapeutic Indications

Symptomatic treatment of abdominal pain and cramps, bowel disturbances and intestinal discomfort related to irritable bowel syndrome.

Treatment of gastro-intestinal spasm secondary to organic diseases.

4.2 Posology and Method of Administration

Duspatalin 200mg, prolonged-release capsules, hard:
The medicinal product is taken orally.
The capsules 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 prolonged release mechanism (see 5.2)

Adults:
One capsule of 200 mg twice daily, to be given one in the morning and one in the evening. Duration of use is not limited.
In case of one or more dose(s) is (are) missed, the patient should continue with the next dose as prescribed; the missed dose(s) is (are) not to 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Administration by children and adolescents below 18.

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4.4 Special Warnings and Precautions for Use

Not applicable

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed with the exception of alcohol. In vitro and in vivo-studies in animals have demonstrated the absence of any interaction between Duspatalin and ethanol.

4.6 Fertility, Pregnancy and Lactation

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

Lactation
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. Duspatalin should not be used during breast-feeding.

Fertility
There are no clinical data regarding impact on male or female fertility; however, available animal studies do not indicate harmful effects of Duspatalin (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 post-marketing 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 events have been reported spontaneously during post-marketing use. A precise frequency cannot be estimated from available data.

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

Immune system disorders: Hypersensitivity (anaphylactic reactions)

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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 local authorities.

4.9 Overdose

Symptoms
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 neurological and cardiovascular nature.

Treatment
No specific antidote is known, and symptomatic treatment is recommended. Gastric lavage should only be considered in case of multiple intoxication 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: A03AA04

Mechanism of action and pharmacodynamic effects
Mebeverine is a mucosotropic antispasmodic with a direct effect 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 might contribute to the local effect of mebeverine on the gastrointestinal tract. Via these mechanisms mebeverine has antispasmodic effects leading to normalization of gut motility without exerting a permanent relaxation of smooth muscle cells in the gastrointestinal tract (so called hypotonia). Systemic side-effects as seen with typical anti-cholinergics are absent.

Clinical efficacy and safety
The clinical efficacy and safety of different formulations of mebeverine was evaluated in more than 1500 patients. Considerable improvements in the predominant symptomatology of irritable bowel syndrome (e.g. abdominal pain, stool characteristics) were generally observed in reference or baseline-controlled clinical studies.

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

Pediatric population
Clinical trials with the tablet or capsule formulations have been performed in adults only. Clinical efficacy and safety data from clinical trials as well as from post-marketing experience with a suspension formulation of mebeverine pamoate in patients > 3 years of age have shown that mebeverine is efficacious, safe and well tolerated.

Clinical studies with mebeverine suspension showed that mebeverine was efficacious in ameliorating the symptoms of irritable bowel syndrome in childhood. Further open, baseline-controlled studies with mebeverine suspension confirmed the efficacy of the drug.

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The dosing schedule for the tablet or capsule formulation was calculated based on the consistent safety and favorable tolerability of mebeverine.

5.2 Pharmacokinetic Properties

Absorption:
Mebeverine is rapidly and completely absorbed after oral administration of tablets or suspension. The prolonged-release formulation permits a twice daily dosing scheme.

Distribution:
No significant accumulation occurs after multiple doses.

Biotransformation:
Mebeverine hydrochloride is mainly metabolized 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 5.77h. During multiple dosing (200 mg b.i.d.) the C_{max} of DMAC is 804 ng/ml and t_{max} is about 3 hrs.
The relative bioavailability of the prolonged-release capsule appears to be optimal with a mean ratio of 97%.

Elimination:
Mebeverine is not excreted as such but metabolized 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
No pharmacokinetic studies have been conducted in children with any formulation of mebeverine.

5.3 Preclinical Safety Data

Effects in repeat-dose studies after oral and parenteral doses were indicative of central nervous involvement with behavioral 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/m2) 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

Duspatalin 200 mg, prolonged-release capsules, hard:
Capsule content (granules):
magnesium stearate
polyacrylate dispersion 30 %
talc hypromellose
methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 %
glycerol triacetate
Capsule shell:
gelatine
titanium dioxide (E171)
printing ink:
shellac (E904) propylene glycol
ammonia solution, concentrated potassium hydroxide
iron oxide black (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years
Do not use after expiration date indicated on box

6.4 Special Precautions for Storage

Not applicable
Store in original container at temperatures from 5°C to 25°C. Keep out of the reach of children.

6.5 Contents of Container

Prolonged-released capsules 200 mg.
15 capsules in PVC/Alu blister. 2 blisters with leaflet in carton box

6.6 Distribution

With prescription

Summary of Product Characteristic
Mebeverine Hydrochloride

MANUFACTURER

Mylan Laboratories SAS
Legal address:
42 Rue Rouget de L'Isle
92150 Suresnes Cedex, France
Site address:
Route de Belleville Lieu dit Maillard, 01400 Châtillon-sur-Chalaronne, France

MARKETING AUTHORIZATION HOLDER

Abbott Healthcare Products B.V.
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