SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Colotal tablets 135 mg

2. Qualitative and quantitative composition

One coated tablet contains 135 mg mebeverine hydrochloride.
Each tablet Duspatal 135 mg contains 79 mg sucrose and 97 mg lactose monohydrate.

For the full list of excipients see section 6.1

3. Pharmaceutical form

coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Irritable bowel syndrome and conditions included in this group such as: chronic irritable colon, gastro-intestinal spasm secondary to organic diseases

4.2 Posology and method of administration

Adults
Colotal tablets should be swallowed with a sufficient amount of water (at least 100 ml water). Do not chew.
One 135 mg tablet three times daily; to be given approx. 20 minutes before meals.

Paediatric Population
Colotal 135 mg tablets are not recommended for use in children and adolescents below 18, due to insufficient data on safety and efficacy.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Since Colotal tablets 135 mg contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Since Colotal tablets 135 mg contain sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions with other medicaments and other forms of interaction

No interactions of mebeverine are known.

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). Colotal is not recommended during pregnancy.

Lactation
It is unknown whether mebeverine or its metaboliltes are excreted in human milk. The excretion of mebeverine in milk has not been studied in animals. Colotal 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 Colotal (see section 5.3).

4.7 Effect 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 can not be estimated from available data.

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

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

Additionally, you can also report to www.Padagis.co.il

4.9 Overdose

In literature there is described very little about symptoms after overdosing with mebeverine. 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 nature. No specific antidote is known and symptomatic treatment is recommended. 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 musulotrophic antispasmodic with a direct effect on the smooth muscle of the gastro-intestinal tract, relieving spasm without affecting normal gut motility. Since this effect is not mediated by the autonomic nervous system, the typical anti-cholinergic side-effects are absent.

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 metabolized by esterases, which split the ester bonds into veratric acid and mebeverine alcohol firstly.

The main metabolite in plasma is DMAC (dementhylated carboxylic acid). The steady state elimination half-life of DMAC is 2.45 h. During multiple dosing the C_{max} of DMAC for the coated tablets with 135 mg is 1670 ng/ml and t_{max} is 1 hr.

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 Pre-clinical safety data

In acute toxicity studies and in various studies with repeat dosing, toxicity of the central nervous system (convulsions) is seen in different animals (rat, dog and rabbit). Dogs seems to be the most sensitive; they react already at oral doses not much higher than human doses. In rats and rabbits the effects can only be seen at doses sufficiently above human doses.

The reproductive toxicity of mebeverine was not sufficiently investigated in animal studies , there have been conflicting results in rats. There were no indication of teratogenic effects in rats and rabbits, however, embryotoxic were noticed in some studies in rats administered 2 fold the human dose. In rats no effects on fertility have been observed. Mebeverine did not show genotoxicity. Carcinogenic potential is not investigated.

6. Pharmaceutical particulars

6.1 List of excipients

Core: lactose monohydrate, potato starch, povidone talc, magnesium stearate
Coating: talc, sucrose, gelatin, acacia, carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

In a cool place, below 25°C.

6.5 Nature and contents of container

Mebeverine hydrochloride coated tablets are supplied in PVC/PVDC blister packages containing 10 per blister and 20, 50, or 100 tablets per pack.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MANUFACTURER and License Holder:
Padagis Israel Pharmaceuticals Ltd.
1st Rakefet st., Shoham

8 LICENSE NUMBER
035-72-25831-00

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