

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.

Excipients with known effect: Lactose and Sucrose.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Round, white sugar 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

The 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.

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: One tablet three times a day, preferably 20 minutes before meals.

Paediatric Population

Mabeverine 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 mebeverine 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 Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The coated tablets contain sucrose, and should not be used by patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency

If this is the first time you have had these symptoms, consult your doctor before using any treatment.

If any of the following apply, do not use mebeverine. It may not be the right treatment for you. See your doctor as soon as possible.

- you are aged 40 years or over
- you have passed blood from the bowel
- you are feeling sick or vomiting
- you are looking pale and feeling tired
- you are suffering from severe constipation
- you have a fever
- you have recently travelled abroad
- you are or may be pregnant
- you have abnormal vaginal bleeding or discharge
- you have difficulty or pain passing urine

Consult your doctor if you have developed new symptoms, or if your symptoms

worsen, or if they do not improve after 2 weeks treatment.

4.5 Interactions 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 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. 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 Mebevirine (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.

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

Additionally, you can also report to www.perrigo-pharma.co.il.

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 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: A03AA04

Mebeverine is a muscolotropic 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 antimuscarinic and phosphodiesterase inhibitory effect might contribute to by the local effect of mebeverine on the gastrointestinal track. 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 the 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/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

Lactose monohydrate, sucrose, potato starch, talc, povidone 25, magnesium stearate, gelatin, acacia spray dried, 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 marketing authorization holder

Perrigo Israel Pharmaceuticals Ltd.

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8 Marketing authorization number

035-72-25831-00

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