Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Colofac 135 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mebeverine Hydrochloride 135mg

Excipients with known effect: also includes Lactose monohydrate 97.0 mg per tablet and Sucrose 79.0 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet.
White, circular, sugar coated tablet.

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

For oral use.
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.

Adults and children over 10 years:
One tablet three times a day preferably 20 minutes before meals.
Duration of use is not limited. However, after a period of several weeks when the desired effect has been obtained, the dosage may be gradually reduced.

In case of missed dose(s), the patient should continue with the next dose as prescribed; do not take the missed dose(s) in addition to the regular dose.

Children under 10 years:
Colofac should not be used in children aged 3 years and younger as no clinical data are available. For children from 3-10 years Colofac 135mg tablets should not be used due to the high content of the active substance.

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

Hypersensitivityto the active substance or to anyof the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prior to treating patients with mebeverine, care should be taken to exclude organic disease of the bowel, particularly malignancy.

Since Colofac 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.

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

4.5 Interaction with other medicinal products and other forms of interactions

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 Colofacand 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). Colofac 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. Colofac should not be used during breast-feeding.

Fertility
There are no clinical dataregarding impact on male or female fertility; however, available animal studies do not indicate harmful effects of Colofac (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 spontaneouslyduring post-marketing use. A precise frequencycannot be estimated from available data.
Allergic reactions mainly but not exclusivelylimited to the skin have been observed.
SkinandSubcutaneous tissue disorders:
Urticaria, angioedema, face oedema, exanthema

Immune system disorders:
Hypersensitivity(anaphylactic reactions).

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 reportanysuspected 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

Symptoms

Theoretically,CNSexcitabilitymayoccur in cases of overdosage.In cases where mebeverine was taken in overdose, symptoms were either absent or mild and usuallyrapidlyreversible. Observedsymptoms of overdose were of neurological and cardiovascular nature.

Treatment

No specific antidote is known and symptomatic treatment is recommended.Gastric lavage shouldonlybe 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 tertiaryamino group, ATC Code: A03AA04

Mechanism of action and pharmacodynamic effects

Mebeverine is a musculotropic 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 motilitywithout 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 efficacyand safety of different formulations of mebeverine was evaluated in more than 1500 patients. Considerable improvements in the predominant syptomatologyof ittitable bowel syndrome (e.g. abdominal pain, stool characteristics) were generallyobserved in reference or baseline-controlled clinical studies.

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

Paediatric population
Clinical trials with the tablet or capsule formulations have been performed in adults only.
Clinical efficacyand safetydata from clinical trials as well as from post-marketing experience with a suspension formulation of mebeverine pamoate > 3years 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 efficacyof the drug.

The dosing schedule for the tablet or capsule formulation was calculated based on the consistent safety and favourable tolerabilityof mebeverine.

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 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 2.45 h. During multiple dosing C_{max} of DMAC for the coated tablets with 135mg is 1670 ng/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 in the urine, mebeverine alcohol is also excreted in 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 behavioural excitation, mainlytremor 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/daybasedonbodysurface area (mg/m2) comparisons. Thereproductive 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 dailyclinical dose. This effect was not observed in rabbits. No effects on male or female fertilitywere noted in rats at doses equivalent to the maximum clinical dose. Inconventionalinvitroandinvivogenotoxicitytestsmebeverinewasdevoidofgenotoxic effects. No carcinogenicitystudies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Starch (potato or maize)
Povidone
Talc
Magnesium stearate

Coating:
Talc
Sucrose
Gelatin
Acacia
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package to protect from light.

6.5 Nature and contents of container

AL/PVC blisters in boxes containing 4 tablets (physician's sample) or 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 February 1983

Date of last renewal: 07 February 2008

10 DATE OF REVISION OF THE TEXT

June 2017