AUSTRALIAN PRODUCT INFORMATION

COLOFAC®

mebeverine hydrochloride tablet

1 NAME OF THE MEDICINE

Mebeverine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COLOFAC tablet contains 135 mg of mebeverine hydrochloride as the active ingredient.

Excipients with known effect: lactose, sugars and traces of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

COLOFAC tablets are sugar-coated, white, round, biconvex, and 11 mm in diameter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

COLOFAC tablets are indicated in the management of the irritable bowel syndrome ('irritable colon', 'spastic colon', 'functional bowel disorders', 'spastic constipation', 'nervous diarrhoea'). COLOFAC is used to treat the symptoms of this condition - i.e. abdominal pain and cramps, persistent, non-specific diarrhoea (with or without alternating constipation) and flatulence.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended adult dose is one COLOFAC mebeverine hydrochloride 135 mg (1 tablet) three times daily, preferably before or with food. In case one or more doses are missed, the patient should continue with the next dose as prescribed, the missed doses are not to be taken in addition to the regular dose.

After a period of several weeks when the desired effect has been obtained, the dosage may be gradually reduced.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Although not reported, COLOFAC tablets should be used with caution in patients with the following conditions on the basis of potential clinical significance:

Pharmaceutical Precaution

COLOFAC tablets contain lactose monohydrate (80 mg per tablet) and consideration should be given to patients with a potential diagnosis of lactose intolerance simulating irritable bowel syndrome. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Cardiac dysrhythmia

In particular patients with partial or complete atrioventricular heart block, and/or angina or severe ischaemic heart disease.

Use in Hepatic Impairment

Hepatic dysfunction i.e. patients with advanced liver disease e.g. cirrhosis (because of metabolic pathway). Liver function tests may be indicated if patient develops gastrointestinal symptoms or jaundice suggesting hepatic sensitivity.

Use in Renal Impairment

Advanced renal disease (because of excretory pathway).

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Section 6.2 – Incompatibilities.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B2

Safe use in pregnancy has not been established relative to adverse effects on foetal development. Therefore, COLOFAC tablets are not recommended during the first trimester of pregnancy, and otherwise risk-benefit must be considered in its use in pregnant women.

Teratogenicity has not been demonstrated in teratology studies in rats and rabbits.

Use in Lactation

Mebeverine is secreted in breast milk (<10 mcg/mL following an oral dose of 100 mg mebeverine hydrochloride). Although problems have not been documented, as a general rule, COLOFAC tablets should not be given to a woman who is breast feeding unless the anticipated benefits outweigh possible risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Because of the low incidence of adverse drug effects reported a meaningful estimate of adverse reactions is difficult to obtain.

The following side effects have been reported in clinical studies: indigestion, heartburn, dizziness, insomnia, anorexia, headache, decrease in pulse rate, constipation, general malaise.

In very rare cases allergic reactions have been reported, in particular, hypersensitivity, urticaria, angioedema, face oedema and exanthem.

Adverse effects reported during post-marketing use have been consistent with those reported in clinical studies, with the following additional side effect reported:

Immune system disorders:

Hypersensitivity (anaphylactic reactions)

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

On theoretical grounds, it may be predicted that CNS excitability might occur in cases of overdosage. Observed symptoms of overdose have included those of neurological and cardiovascular nature.

No specific information is available on the treatment of overdosage of mebeverine hydrochloride and no specific antidote is available. Therapy with COLOFAC tablets should be discontinued, and the patients' vital functions monitored closely. Treatment is symptomatic and supportive.

For more information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Category: Antispasmodic; smooth muscle relaxant.

Mechanism of Action

Mebeverine has a direct non-specific relaxant effect on vascular, cardiac, and other smooth muscle. Studies indicate that the spasmolytic activity of mebeverine is not restricted to one particular system, but the compound possesses a polyvalent spasmolytic action in which at least three types of mechanisms are involved:

- a direct musculotropic action involving calcium ion exchange and stabilization of excitable membranes;
- a competitive antimuscarinic activity of about 0.05 - 0.1 times that of atropine;
- a local anaesthetic activity together with potentiation of sympathetic inhibitory influences due to blockade of noradrenaline uptake into sympathetic nerve endings.

In *in vitro* studies mebeverine hydrochloride has been shown to have a papaverine-like spasmolytic effect on the smooth muscle of the ileum, uterus and the gall bladder. It possesses a strong local anaesthetic activity.

When tested *in vivo* in various species, mebeverine hydrochloride was found to be three to five times more powerful than papaverine in blocking spasm of smooth muscle and in relieving the carbachol-induced spasm of the sphincter of Oddi in rabbits, mebeverine hydrochloride proved to be twenty times more active than papaverine. *In vivo* studies also demonstrate that mebeverine has only minor effects on normal intestinal peristalsis but possesses spasmolytic activity when hypermotility is induced. The spasmolytic activity is found in all parts of the gastrointestinal tract and, in some experiments, has been found to be more active on colonic smooth muscle.

Studies with mebeverine hydrochloride 100 mg tablets indicate that mebeverine is free of central anticholinergic effects, and practically free of peripheral effects with an activity of less than 0.001 times that of atropine. Mebeverine does not show central depressant or analgesic effects, and only in high doses are some central stimulating effects observed. No ganglion blocking or interference with neuromuscular transmission occurs.

Mebeverine injected intravenously in animals produces transient cardiac arrhythmias, bradycardia and ECG changes.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of ^{3}H and ^{14}C labelled mebeverine hydrochloride in man, absorption was followed by the appearance in the plasma of veratric acid and an oxidised metabolite of the mebeverine alcohol moiety of the drug, mebeverinic acid.

Distribution

Maximum plasma radioactivity levels were found 1-3 hours after dosing. Binding of mebeverine to human serum albumin was 75%.

Metabolism

The primary metabolic step in mebeverine degradation is hydrolysis of the ester function.

Excretion

The major route of excretion of the metabolites is via the urine (95%) and the peak rate of excretion usually occurs within two hours. Virtually 98% urinary recovery of the conjugated and unconjugated metabolites was observed after a period of 24 hours. No unchanged mebeverine was excreted with the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

COLOFAC tablets also contain acacia, carnauba wax, gelatin, lactose monohydrate, magnesium stearate, povidone, potato starch, sucrose and purified talc.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Blister pack [PVC/Al].

Pack sizes: 10, 30 and 90 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 79335 – COLOFAC mebeverine hydrochloride 135 mg tablet blister pack

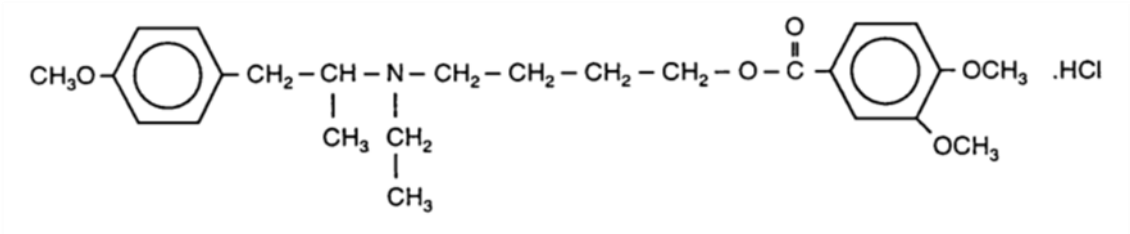
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mebeverine hydrochloride is 4-[ethyl-[2-(4-methoxyphenyl)-1-methylethyl] aminobutyl veratrate hydrochloride, a derivative of -phenylethylamine. It is a white to almost white, crystalline powder having a very bitter taste, very soluble in water, freely soluble in ethanol and practically insoluble in ether. The empirical formula is $C_{25}H_{35}NO_5$.HCl. MW: 466.0

Chemical Structure



CAS Number

3625-06-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

16/05/1987

10 DATE OF REVISION

04/02/2022

Summary Table of Changes

Section Changed	Summary of New Information
2	Editorial update
6.5	Updated information on container and inserted AUST R numbers
8	Update to sponsor details

COLOFAC® is a Viatris company trade mark

COLOFAC_pi\Feb22/01