PRODUCT INFORMATION
COLOFAC®

NAME OF THE MEDICINE

Non-proprietary Name
Mebeverine hydrochloride

Chemical Structure

CAS Number
3625-06-7

DESCRIPTION
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
Each Colofac tablet contains mebeverine hydrochloride 135 mg. The tablets also contain acacia, carnauba wax, gelatine, lactose monohydrate, magnesium stearate, povidone, potato starch, sucrose and purified talc.

PHARMACOLOGY

Pharmacodynamics
Category: Antispasmodic; smooth muscle relaxant.
Mebeverine has a direct non-specific relaxant effect on vascular, cardiac, and other smooth muscle. Studies indicate that the spasmytic activity of mebeverine is not restricted to one particular system, but the compound possesses a polyvalent spasmytic 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 spasmytic 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 spasmytic activity when hypermotility is induced. The spasmytic 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.

**Pharmacokinetics**

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. Thus, the primary metabolic step in mebeverine degradation is hydrolysis of the ester function. Maximum plasma radioactivity levels were found 1-3 hours after dosing. Binding of mebeverine to human serum albumin was 75%. 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.

**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.

**CONTRAINDICATIONS**

Hypersensitivity to any component of the product.

**PRECAUTIONS**

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

- Cardiac dysrhythmia; in particular patients with partial or complete atrioventricular heart block, and/or angina or severe ischaemic heart disease.
- 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.
- Advanced renal disease (because of excretory pathway).
- 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.
Use in 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.

ADVERSE 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)

DOSAGE AND 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.

OVERDOSAGE
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.

In case of overdose, contact the Poisons Information Centre on 13 11 26 for advice on management.
PRESENTATION AND STORAGE CONDITIONS
Colofac tablets are sugar-coated, white, round, biconvex, and 11 mm in diameter. Colofac tablets are available in cartons of 10, 30 and 90 tablets in blister packs.
Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Mylan Health Pty Ltd
Level 1, 30-34 Hickson Road
Miller Point, NSW 2000
Australia
www.mylan.com.au
Phone: 1800 314 527

POISON SCHEDULE OF THE MEDICINE
Schedule 4

DATE OF APPROVAL
16 May 1987

DATE OF MOST RECENT AMENDMENT
24 August 2017