AUSTRALIAN PRODUCT INFORMATION
APO-MEBEVERINE
Mebeverine hydrochloride

1 NAME OF THE MEDICINE

Mebeverine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each APO-MEBEVERINE tablet contains mebeverine hydrochloride 135 mg.

Excipients with known effect: lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

APO-MEBEVERINE tablets are white, round, biconvex, film coated and plain on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APO-MEBEVERINE tablets are indicated in the management of the irritable bowel syndrome ('irritable colon', 'spastic colon', 'functional bowel disorders', 'spastic constipation', 'nervous diarrhoea'). APO-MEBEVERINE 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 APO-MEBEVERINE 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, APO-MEBEVERINE 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.

Pharmaceutical Precaution - APO-MEBEVERINE tablets contain lactose monohydrate 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.

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

No data available

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, APO-MEBEVERINE tablets are not recommended during the first trimester of pregnancy, and otherwise risk-benefit must be considered in its use in pregnant women.

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 APO-MEBEVERINE 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, angiodema, 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 APO-MEBEVERINE tablets should be discontinued, and the patients vital functions monitored closely. Treatment is symptomatic and supportive.

For 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

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

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains microcrystalline cellulose, lactose monohydrate, sodium starch glycolate A, povidone, magnesium stearate, purified talc and OPADRY complete film coating system 03F58763 WHITE.

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 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

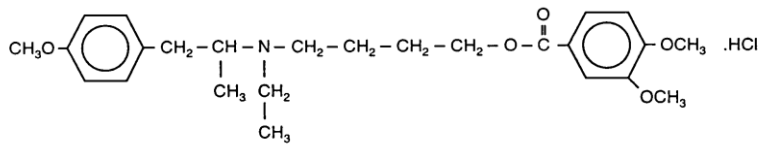
APO-MEBEVERINE tablets are available in cartons of 10, 30 and 90 tablets in PVC/PVDC/Al blister packs

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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

CAS number

2753-45-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

Tel: (02) 8877 8333
http://www.apotex.com/au

9 DATE OF FIRST APPROVAL

03 April 2018

10 DATE OF REVISION

30 January 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Change in Sponsor address