PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Mebeverine hydrochloride

Chemical name: (RS)-4-[ethyl(4-methoxy-a-methylphenethyl)amino]butyl veratrate hydrochloride

Structural formula:

Molecular formula: C_{25}H_{35}NO_{5}.HCl          Molecular weight: 466

CAS Registry No.: 2753-45-9

DESCRIPTION

Mebeverine hydrochloride is a white to almost white, crystalline powder having a very bitter taste. It is very soluble in water, freely soluble in ethanol and practically insoluble in ether.

Each tablet contains 135 mg mebeverine hydrochloride as the active ingredient. The tablets also contain the following inactive ingredients: magnesium stearate, sodium starch glycollate, purified talc, povidone, microcrystalline cellulose, lactose (100 mg/tablet), Opadry White Y-1-7000 (ARTG No. 2731) (includes hypromellose, macrogol 400, titanium dioxide CI77891).

PHARMACOLOGY

Pharmacodynamics

Antispasmodic; smooth muscle relaxant.

Mebeverine has a direct nonspecific 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:

1. A direct musculotropic action involving calcium ion exchange and stabilisation of excitable membranes;
2. A competitive antimuscarinic activity of about 0.05 to 0.1 times that of atropine;
3. 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 spasmylytic 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 3 to 5 times more powerful than papaverine in blocking spasm of smooth muscle. In relieving the carbachol-induced spasm of the sphincter of Oddi in rabbits, mebeverine hydrochloride proved to be 20 times more active than papaverine. *In vivo* studies have also demonstrated 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.

**Pharmacokinetics**

Following oral administration of $^3$H- and $^{14}$C-labelled mebeverine hydrochloride in humans, 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 to 3 hours after dosing. Binding of mebeverine to human serum albumin is 75%.

The major route of excretion of the metabolites is via the urine (95%) and the peak rate of excretion usually occurs within 2 hours. Virtually 98% urinary recovery of the conjugated and unconjugated metabolites is observed after a period of 24 hours. No unchanged mebeverine is excreted in the urine.

**INDICATIONS**

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

**CONTRAINdications**

Hypersensitivity to any component of this product.

**PRECAutions**

Although not reported, Colese 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.* Patients with advanced liver disease, eg. 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. Colese tablets contain lactose (100 mg/tablet) and consideration should be given to patients with a potential diagnosis of lactose intolerance simulating the 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 Pregnancy (Category B2)

Safe use in pregnancy has not been established relative to adverse effects on foetal development. Therefore, Colese 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.

Australian categorisation definition of Category B2. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Use in Lactation

Mebeverine is secreted in breast milk (<10 microgram/mL following an oral dose of 100 mg mebeverine hydrochloride). Although problems have not been documented, as a general rule Colese tablets should not be given to a woman who is breastfeeding 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 135 mg (1 tablet) three times daily, preferably taken before or with food.

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

OVERDOSAGE

No data are available in regard to overdosage in humans. 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 with mebeverine hydrochloride and no specific antidote is available. Therapy with Colese tablets should be discontinued, and the patient's vital functions should be closely monitored.

Treatment is symptomatic and supportive.

In case of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

**Colese**, 135 mg tablet: white, film coated, marked "MV 135" on one side, and blank on the other; 30's, 90's.

Store below 30°C.

POISON SCHEDULE OF THE MEDICINE

S4  Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

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30-34 Hickson Road
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www.alphapharm.com.au

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29/04/1997

DATE OF MOST RECENT AMENDMENT

12 April 2013