NEW ZEALAND DATA SHEET

1. Product Name

Mebeverine (Arrotex Pharmaceuticals), 135 mg, Film-coated tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 135 mg of mebeverine hydrochloride.

Excipients with known effect: lactose and sucrose. For the full list of excipients, see **section 6.1.**

3. Pharmaceutical Form

Mebeverine tablets are white, round, biconvex, film-coated tablets and plain on both sides with a diameter of 11.2mm.

4. Clinical Particulars

4.1 Therapeutic indications

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

Dose

Adults

The recommended adult dosage is one mebeverine hydrochloride 135 mg tablet three times daily, preferably 20 minutes before meals. 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 mebeverine.

4.4 Special warnings and precautions for use

Although not reported, 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.
- Hepatic dysfunction i.e. patients with advanced liver disease e.g. cirrhosis (because of metabolic pathway). Liver function tests may be indicated if patients develop gastrointestinal symptoms or jaundice suggesting hepatic sensitivity.
- Advanced renal disease (because of metabolic pathway).

Pharmaceutical Precaution

Mebeverine tablets contain lactose (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.

4.5 Interaction with other medicines and other forms of interaction

No data available.

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category B2)

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

Breast-feeding

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, mebeverine tablets should not be given to woman who is breastfeeding unless the anticipated benefits outweigh possible risks.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Because of the low incidence of adverse 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 exanthema.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 Mebeverine tablets should be discontinued, and the patients vital functions monitored closely. Treatment is symptomatic and supportive.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for Functional Gastrointestinal Disorders, ATC code: A03AA04

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

Mebeverine has a direct non-specific relaxant effect on vascular, cardiac and other smooth muscle.

Mechanism of action

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 Ca^{++} ion exchange and stabilisation 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.

Clinical efficacy and safety

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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of 3H and 14C 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. The plasma halflife of these metabolites is about 2 hours.

Maximum plasma radioactivity levels were found 1-3 hours after dosing.

Distribution

75% of mebeverine binds to human serum albumin.

Biotransformation

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

Elimination

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

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

6. Pharmaceutical Particulars

6.1 List of excipients

Mebeverine tablets contain the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry complete coating film coating system 03F58763 WHITE (Hypromellose, titanium dioxide, polyethylene glycol and talc), Povidone, purified talc and Sodium starch glycollate type A.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25℃.

6.5 Nature and contents of container

Blister pack. Pack-sizes of, 10, 30 and 90 tablets.

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Arrotex Pharmaceuticals (NZ) Limited
C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street
Wellington 6011
New Zealand

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9. Date of First Approval

19 July 2019

10. Date of Revision of the Text

19 April 2023

Summary table of changes

Section Changed	Summary of new information
8	Sponsor details update