

# NEW ZEALAND DATA SHEET

COLOFAC®



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## 1. Product Name

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Colofac, 135 mg, Tablet.

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## 2. Qualitative and Quantitative Composition

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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.

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## 3. Pharmaceutical Form

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

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  $C_{25}H_{35}NO_5 \cdot HCl$ . MW: 466.0

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## 4. Clinical Particulars

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### 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*

#### **Dose**

#### **Adults**

The recommended adult dosage is one Colofac 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, 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 patients develop gastrointestinal symptoms or jaundice suggesting hepatic sensitivity.
- Advanced renal disease (because of metabolic pathway).

#### **Pharmaceutical Precaution**

Colofac 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 Colofac 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, Colofac 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 Colofac 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).

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## **5. Pharmacological Properties**

### **5.1 Pharmacodynamic properties**

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

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<sup>++</sup> 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 <sup>3</sup>H and <sup>14</sup>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. The plasma half-life 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.

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

Colofac tablets contain the following inactive ingredients: acacia, carnauba wax, gelatin, lactose, magnesium stearate, povidone, potato starch, sucrose and purified talc.

Gelatin raw material may contain sulfur dioxide residue. Colofac is gluten free.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

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

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Not applicable.

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## **7. Medicines Schedule**

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Prescription Medicine

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## **8. Sponsor Details**

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Mylan New Zealand Ltd  
PO Box 11-183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## **9. Date of First Approval**

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17 July 1967

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## **10. Date of Revision of the Text**

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14 June 2017	Summary of Changes: Sponsor transfer. Storage temperature change. Additional note on sulfur dioxide. Revised to SmPC format.
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