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	Doc No. BML/PRT/S013	Date rev 09/2020	Next rev date: 08/2025

Summary of Product Characteristics

For

Paraton syrup

(Paracetamol + Chlorpheniramine maleate + Ascorbic acid)

1. NAME OF MEDICINAL PRODUCT

Paraton syrup

2. QUALITATIVE AND QUANTITATIVE DESCRIPTION

Each 5ml of the syrup contains

Paracetamol	120mg
Chlorpheniramine maleate	2mg
Ascorbic acid	40mg

3. PHARMACEUTICAL FORM

Light yellow oral preparation presented as sugar-based syrup and flavoured in 100ml amber PET bottle covered ROPP cap with dose measurement cap to facilitate easy dosing

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paraton is formulated for acute symptomatic treatment of pain and fever associated with rhinopharyngitis and rhinitis.

4.2 Posology and method of administration

Posology

The recommended daily dose is age dependent. There should be at least 4 hours interval between intakes. In case of flu it is best to take Paraton with warm water in the evening. The treatment period should not exceed 3 days.

Renal insufficiency

In case of severe renal insufficiency (creatine clearance below 10ml/min), the interval between the intakes should be at least a minimum of 8 hours.

Hepatic insufficiency

Caution should be exercised in patients suffering from impaired hepatic function.

Chronic alcoholism

The maximum daily dose in patients suffering from chronic alcoholism is 2 g paracetamol, an equivalent of 85ml of the syrup. The interval between the intakes should be at least a minimum of 8 hours.

The safety and efficacy of promethazine hydrochloride used in the formulation of Biothazine syrup has been established in adults and paediatric populations when taken at the prescribed doses

Method of Administration- For oral use

Age group	**Dose**
<1yr	Not recommended
1-2yr	2.5ml twice daily; maximum up to 5ml daily
2-6yrs	2.5ml every 4-6hrs; max up to 15ml daily
6-12yrs	5ml every 4-6hrs daily; max up to 30ml daily
>12yrs	10ml every 4-6hrs daily; max up to 60ml daily

Or as directed by the physician.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients

Hepatocellular insufficiency

- Closed-angle glaucoma

- Urinary retention in connection with uretero-prostatic problems

- Use in patients who are currently taking or have taken monoamine oxidase inhibitors (MAOIs) within the last 2 weeks

4.4 Special warnings and Precautions for Use

Medical supervision is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

In case of high or persistent fever, if superinfection occurs or if the symptoms persist for more than 3days, a new treatment should be taken in consideration.

The risk of mainly psychological dependence does not appear unless the doses are higher than recommended or unless the product is taken in course of long treatments.

To avoid the risk of overdosing, other medicines containing paracetamol should be avoided. In adults weighting over 50 kg the overall daily dose should not exceed 4 grams in one day

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage.

Caution is advised in patients with asthma who are sensitive to acetylsalicylic acid, since mild bronchospasms are reported in association with paracetamol (cross reaction).

Avoid drinking of alcoholic beverages or the use of sedatives (particularly barbiturates) during the treatment because they may increase the potential sedative effect of antihistamines.

In susceptible patients for chlorpheniramine maleate, antimuscarinic effect may cause increased intraocular pressure, exacerbation of lower urinary tract obstruction and impaired gastric evacuation e.g. Pyloric stenosis.

Caution is advised in the administration to patients with glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia, disorders of iron metabolism (Gilbert's syndrome), urinary calculus, (don't use more than 1 g ascorbic acid per day), dehydration, alcohol abuse and chronic malnutrition.

Each 10ml contains 3.5 g of sucrose – for consideration in patients with diabetes or in case of low-sugar diets. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Drug Interactions

Paracetamol

Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, anticonvulsants such as phenytoin, phenobarbital, methylphenobarbital and primidone, rifampicin, St. John's Wort (Hypericum perforatum), monoamine oxidase inhibitors and

tricyclic antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

The rate of absorption of paracetamol may be decreased by anticholinergic drugs (e.g., glycopyrronium, propantheline), and increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Isoniazide reduces paracetamol clearance with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect. Probenecid reduces clearance of paracetamol by inhibiting conjugation with glucoronic acid.

Regular use of paracetamol possibly reduces metabolism of zidovudine (increased risk of neutropenia).

The elimination half-life of chloramphenicol may be prolonged by paracetamol.

Chlorpheniramine maleate

Alcohol

The sedative effect of antihistamine H1is increased by alcohol. The reduced alertness may make driving vehicles and using of machines dangerous. Avoid alcoholic beverages and medicines containing alcohol.

Sedative drugs

Morphine derivatives (analgesics, anti-cough medicines and substitutive treatments, neuroleptics, barbiturates, benzodiazepines, anxiolytic other than benzodiazepines (for example meprobamate), hypnotic, antidepressive sedatives (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine, sedative H1 antihistamines, central antihypertensives, thalidomide and baclofen may increase central depression. The reduced alertness may make driving vehicles and using of machines dangerous.

M-cholinoblockers

Tricyclic antidepressants, most sedative antihistamines, anticholinergic antiparkinsonian agents, anticholinergic antispasmodic agents, disopyramide, phenothiazine neurolepticsas

well as clozapine. Other undesirable atropine effects like urine retention, constipation, and dry mouth can occur.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate evidences that any of the active substances of Paraton is harmful to foetus, though it can have side effects such as feeling drowsy. Paraton can thus be safely used in pregnancy, but your doctor may prefer a non-drowsy anti-histamine like Loratidine before Chlorpeniramine maleate.

Lactation

There are no adequate evidences that any of the active substances of Paraton is harmful to foetus, though it can have side effects such as feeling drowsy which may reduce milk supply to baby. Consult with your doctor or pharmacist to know if a non-drowsy antihistamine like Loratidine would be preferred.

4.7 Effects on ability to drive and use machine

Paraton should not be taken in this case as some of the active ingredients of Paraton can cause drowsiness.

4.8 Undesirable effects

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (about 1 of 10 persons), common (about 1 of 100 persons to about 1 of 10 persons), uncommon (about 1 of 1,000 persons to about 1 of 100 persons), rare (about 1 of 10,000 persons to about 1 of 1,000 persons), very rare (about 1 of 10,000 persons), not known (cannot be estimated from the available data).

Chlorpheniramine maleate

Blood and lymphatic system disorders

Not known: leukopenia, neutropenia, thrombocytopenia, hemolytic anemia.

Immune system disorders

Rare: erythema, itching, eczema, purpura, urticaria, edema, angioedema, anaphylactic shock.

Psychiatric disorders

Not known: agitation, anxiety, insomnia, mental confusion, hallucinations and memory or ability to concentrate drop (especially in the elderly).

Nervous system disorders

Not known: sleepiness (especially at the beginning of treatment), vertigo, impaired coordination of movements, tremor.

Eye disorders

Not known: abnormal accommodation, mydriasis.

Vascular disorders

Not known: orthostatic hypotension.

Gastrointestinal disorders

Not known: constipation.

Renal and urinary disorders

Not known: urinary retention.

Paracetamol Blood and lymphatic system disorders

Very rare: thrombocytopenia, leucopenia, neutropenia.

Immune system disorders

Rare: hypersensitivity reactions - angioedema, anaphylactic shock.

Skin and soft tissue disorders Rare: skin rash, urticarial Very rare: serious skin reactions

Ascorbic acid

Renal and urinary disorders

Not known: oxalate and urate stones (from more than 1 g doses).

Blood and lymphatic system disorders Not known: Increased chronic hemolysis (if lack of glucose-6-phosphate dehydrogenase).

4.9 Overdose

Promethazine in overdose appears principally to cause central nervous system depression and anticholinergic effects including delirium, agitation and hallucinations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antiemetic

ATC code:

Mechanism of Action/Pharmacodynamics effects

Promethazine is a phenothiazine antihistamine, antagonizing the central and peripheral effects of histamine mediated by histamine H1 receptors. Antihistamines competitively antagonize most of the smooth muscle stimulating actions of histamine on the H1 receptors of the gastrointestinal tract, uterus, large blood vessels, and bronchial muscle. Increased capillary permeability and oedema formation, flare and pruritus, resulting from actions of histamine H1 receptors are also effectively antagonized. The antiemetic effect of promethazine may be due to the blockade of dopaminergic receptors in the chemoreceptor trigger zone (CTZ) of the medulla.

Promethazine is an antagonist of histamine H1, post-synaptic mesolimbic dopamine, alpha adrenergic, muscarinic and NMDA receptors. Its effectiveness in relieving motion sickness and vomiting comes from its antagonism of central and peripheral histamine mediated by H1 receptors

5.2 Pharmacokinetics Properties

Absorption

Promethazine hydrochloride is well absorbed from the GIT. Peak plasma concentrations occur after 2 to 3 hours when promethazine is administered orally or intramuscularly. Following rectal administration, peak plasma concentrations were observed after about 8 hours.

Oral bioavailability is approximately 25%. Rectal bioavailability has been reported to be 23%

Distribution

Promethazine is widely distributed in body tissues and has a large apparent volume of distribution following oral and intramuscular administration. Promethazine has been reported to be 93% protein bound and it readily crosses the placenta, appearing in the cord blood within 1.5minutes when given intravenously at term.

Metabolism

Promethazine is principally metabolized to promethazine sulphoxide and to a lesser degree desmethylpromethazine. It was shown that the peak plasma concentrations of the sulphoxide metabolite occurred earlier after oral administration than after intravenous administration. It was concluded that the major site of metabolism is the liver and that the drug substance is subjected to extensive biotransformation, explaining the oral bioavailability of 25%. Metabolism also occurs in the gut wall but to a lesser degree.

Elimination

Elimination of promethazine is primarily due to hepatic metabolism. After oral ingestion, only about 0.6% of an administered dose is excreted unchanged in the urine within 24 hours, while 10.3% was excreted as promethazine sulphoxide. The renal clearance of the sulphoxide approached the GFR being 90ml/min while that of promethazine was only 5.9ml/min, suggesting significant tubular reabsorption of promethazine. Most oxidized metabolites of other phenothiazines are biologically inactive. No evidence was found to suggest that metabolites of promethazine are pharmacologically or toxicologically active. Promethazine has not been reliably detected in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sucrose, Sodium benzoate, Aspartame, Citric acid, Pineaple flavour, Carmosine red

6.2 Incompatibilities

Biothazine should not be mixed with any other medicinal products, as compatibilities study has not been carried out

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

Biothazine should be stored in a cool dry place at temperatures not more than 30^{o}C

6.5 Nature and Contents of Container

Plain Amber-coloured Polyethylene terephthalates (PET) bottle with ROPP cap placed inside a paperboard carton

6.6 Special Precautions for disposal

Container and/or any unused product should be disposed in accordance with the local requirement

7. MANUFACTURER

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