PROFESSIONAL INFORMATION for PARAGRIP C

SCHEDULING STATUS:

S2

PROPRIETARY NAME AND DOSAGE FORM:

PARAGRIP C effervescent tablets

COMPOSITION:

Active Ingredients

Each tablet contains:

Paracetamol	500 mg
Sodium ascorbate equivalent to Vitamin C	250 mg
Chlorphenamine maleate	2 mg

Inactive Ingredients

Anhydrous citric acid, aspartame, lemon flavour, orange flavour, povidone K30, simethicone, sodium carbonate anhydrous, sodium hydrogen carbonate and sorbitol.

PARAGRIP C contains the sugar alcohol, sorbitol.

PHARMACOLOGICAL CLASSIFICATION:

A.5.8. Preparations for the common cold including nasal decongestants.

PHARMACOLOGICAL ACTION:

PARAGRIP C effervescent tablets have analgesic, antipyretic and antihistaminic properties.

PARAGRIP C is a combination of the following:

Chlorphenamine maleate

Pharmacodynamic properties:

Chlorphenamine maleate is a reversible H_1 receptor antagonist which inhibits the interaction of histamine with H_1 receptors. H_1 antagonists inhibit most of the effects of histamine on smooth muscles, especially the constriction of respiratory smooth muscle. H_1 antagonists suppress histamine – evoked salivary lacrimal and other exocrine secretions.

Pharmacokinetic properties

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentration occurring about 2,5 to 6 hours after administration by mouth and the effects usually last 4 – 6 hours.

Bioavailability is low, values of 41 ± 16 % having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. Unchanged chlorphenamine and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. About 70 % ± 3 % of chlorphenamine in the circulation is bound to plasma proteins. The half-life in adults is 20 ± 5 hours but elimination is much more rapid in children. Chlorphenamine is widely distributed in the body, and enters the CNS.

Paracetamol

Pharmacodynamic properties

Paracetamol has analgesic and antipyretic effects.

Pharmacokinetic properties

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0,5 to 1 hour. The plasma half-life is about 2 hours. Plasma protein binding is variable. Paracetamol is relatively uniformly distributed throughout most body fluids.

Paracetamol is metabolised in the liver primarily by conjugation with glucuronic acid (about

60 %), sulphuric acid (about 35 %) or cysteine(about 3 %); small amounts of hydroxylated and deacetylated metabolites also have been detected. Paracetamol is renally excreted primarily as conjugated metabolities. Some 90 % to 100 % of the substance may be recovered in the urine within the first day at therapeutic dosing.

Children have less capacity for glucuronidation of the substance than do adults.

Sodium ascorbate

Pharmacodynamic properties

A vitamin supplement.

Pharmacokinetic properties

Sodium ascorbate is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissue. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Excess of the body's needs is rapidly eliminated unchanged in the urine. Ascorbic acid crosses the placenta and is distributed into breast milk.

INDICATIONS

PARAGRIP C is indicated for symptomatic relief of runny nose, sneezing, sore throat, headache and generalized aching due to colds and flu.

CONTRAINDICATIONS

PARAGRIP C is contraindicated in:

- Hypersensitivity to chlophenamine maleate, paracetamol, sodium ascorbate or any of the ingredients of PARAGRIP C (see **COMPOSITION**).
- Severe liver function impairment.

- Epilepsy.
- Children under the age of 12 years.
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

Chlorphenamine maleate

PARAGRIP C should be used with caution in patients with prostatic hypertrophy, narrow angle glaucoma, emphysema or chronic bronchitis, porphyria. Paradoxical hyperexcitability, nervousness and insomnia may occur in children and in the elderly. Elderly patients are especially susceptible to dizziness, sedation, confusion, hypotension and anticholinergic effects such as dry mouth and urinary retention.

PARAGRIP C should be used with care in patients with pyloroduodenal obstruction,epilepsy and severe cardiovascular disorders.

Paracetamol

Dosages of **PARAGRIP C** in excess of those recommended may cause severe liver damage. Consult a medical practitioner if pain or fever persists or gets worse at the recommended symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition. Do not use **PARAGRIP C** continuously for more than 10 days without consulting your doctor.

PARAGRIP C contains paracetamol which may be fatal in overdosage. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Dosages in excess of those recommended may cause severe liver damage. Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take

excessive quantities of **PARAGRIP C**. Use with caution in renal disease.

Effect on the ability to drive and use machines

PARAGRIP C may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants Patients should. be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

Information on excipients of PARAGRIP C:

PARAGRIP C contains the sugar alcohol, sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

INTERACTIONS

Paracetamol:

Hepatotoxic medicines such as isoniazid – Increased risk of hepatotoxicity.
Enzyme inducing medicines – Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of **PARAGRIP C**. Metoclopramide – Absorption of **PARAGRIP C** may be accelerated. Chlorphenamine – Absorption of **PARAGRIP C** is reduced if given within one hour of chlorphenamine. Prolonged concurrent use of **PARAGRIP C** with salicylates increases the risk of adverse renal effects. Excretion may be affected and plasma concentrations altered when given with probenecid.

Chlorphenamine Maleate

Chlorphenamine maleate may enhance the sedative effect of central nervous system depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and antipsychotics.

Concurrent use of MAO inhibitors may prolong and intensify the anticholinergic and CNS depressant effect of chlorphenamine maleate.

Concurrent use is not recommended. Care should be observed when tricyclic antidepressants, maprotiline, monoamine oxidase inhibitors, guanethidine, reserpine, methyldopa and atropine are taken concomitantly. Chlorphenamine maleate given with ototoxic medication may mask the symptoms of ototoxicity such as tinnitus, dizziness or vertigo.

Chlorphenamine may increase the risk of phenytoin toxicity.

Vitamin C

Vitamin C should not be given for the first month after starting treatment with desferrioxamine due to increased iron toxicity.

Large doses of Vitamin C may increase serum ethinylestradiol concentrations in women taking oral contraceptives.

Concomitant use of Vitamin C and fluphenazine may result in decreased serum concentrations of fluphenazine.

May interact with warfarin.

PREGNANCY AND LACTATION

The safety and efficacy in pregnancy and lactation has not been established (See **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over 12 years: One tablet every 8 hours if necessary. Dissolve one tablet in a glass of water and drink the contents immediately once the whole tablet has dissolved.

SIDE EFFECTS

Paracetamol:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders:	Less frequent:	Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia and anaemia.
Hepato-biliary disorders:	Less frequent: Frequency unknown:	Hepatitis. Pancreatitis.
Skin and subcutaneous tissue disorders:	Less frequent: Frequency unknown:	Allergic dermatitis. Dermatitis, skin rashes and other allergic reactions. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions.
Renal and urinary disorders:	Frequency unknown:	Renal colic, renal failure and sterile pyuria.

Chlorphenamine maleate

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders:	Less frequent:	Blood dyscrasias, including agranulocytosis, leukopenia, haemolytic anaemia and thrombocytopenia.

Immune system disorders:	Less frequent:	Anaphylaxis including tightness of the chest, hypersensitivity reactions (including bronchospasm, angioedema).
Psychiatric disorders:	Frequency unknown:	Depression.
Nervous system disorders:	Frequent: Less frequent: Frequency unknown:	Drowsiness. Central nervous system reactions include sedation, convulsions or seizures, dizziness, fatigue, increased sweating, abnormal coordination, tremor lassitude, euphoria, nervousness, insomnia and headache. Confusion, hallucinations, paraesthesias and ataxia.
Eye disorders:	Less frequent:	Blurred vision, diplopia.
Ear and labyrinth disorders:	Less frequent:	Tinnitus.
Cardiac disorders:	Less frequent: Frequency unknown:	Hypotension, palpitations, dysrhythmia and tachycardia. Hypertension, tightness of the chest, tingling, heaviness and weakness of the hands.
Respiratory, thoracic and mediastinal disorders:	Less frequent: Frequency unknown:	Thickening of mucous. Dryness of the respiratory passages.

Gastrointestinal disorders:	Frequent: Frequency unknown:	Dryness of mouth, nose or throat, gastrointestinal upset, loss of appetite, constipation, diarrhoea, nausea, vomiting. Epigastric pain and gastric reflux.
Hepato-biliary disorders:	Less frequent:	Cholestasis, hepatitis or other hepatic function abnormalities.
Skin and subcutaneous tissue disorders:	Less frequent: Frequency unknown:	Exfoliative dermatitis. Photosensitivity and skin rash, allergic dermatitis, drug fever, hair loss and sweating.
Musculoskeletal, connective tissue and bone disorders:	Frequency unknown:	Extrapyramidal effects with muscle spasms and dystonia, myalgia.
Renal and urinary disorders:	Less frequent: Frequency unknown:	Difficult or painful urination, dysuria, urinary retention. Urinary frequency.
General disorders and administrative site conditions:	Less frequent:	Oedema

Vitamin C

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders:	Frequency unknown:	Ascorbic acid in large doses may result in haemolysis in patients with glucose-6-dehydrogenase deficiency.

Gastrointestinal disorders:	Less frequent:	Large doses are reported to cause diarrhoea and other gastro-intestinal disturbances.
Renal and urinary disorders:	Frequency unknown:	Large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi. Vitamin C should be given with care to patients with hyperoxaluria. Tolerance may be produced with prolonged use of large doses.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF

ITS TREATMENT:

Paracetamol:

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 – 10 g/day) of Paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting,

anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment of paracetamol overdosage:

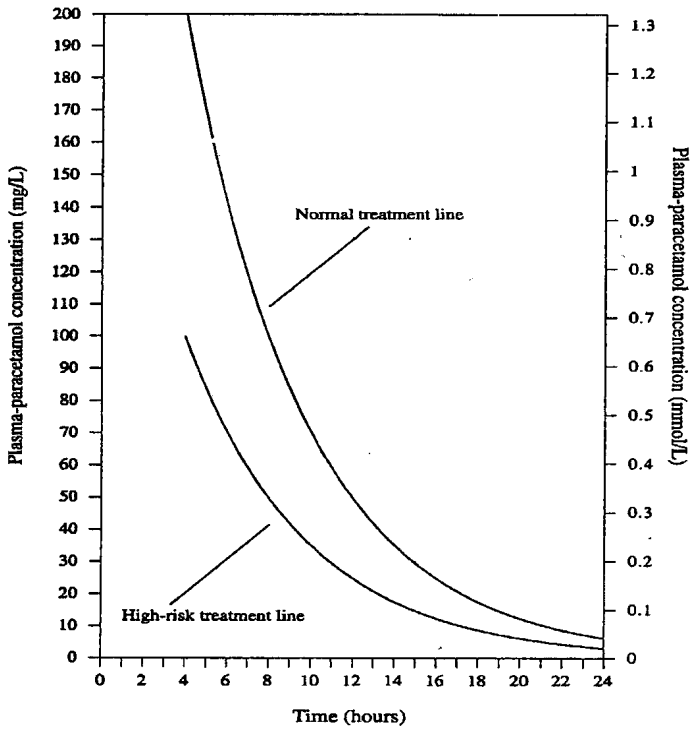
Although evidence is limited it is recommended that any adult person who has ingested 5 – 10 grams or more of paracetamol (or child who has had more than 140 mg/kg) within the preceding four hours, should have stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning(see above). In patients who are stuperose or comatose endotracheal intubations should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administrated to all cases of suspected overdose as soon as possible preferably within eight hours of overdose, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes, followed by infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1000 ml dextrose injection over the next sixteen hours. **The volume of the intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administrated initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdose. Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage and hence requiring continued treatment with N-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

Figure 1. A linear plot of plasma-paracetamol concentration against hours after ingestion:



1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.

4. Patients whose plasma-paracetamol concentrations are above the normal treatment line should be treated.
5. Patients on enzyme-inducing medication or with malnutrition or a history of alcohol abuse should be treated if their plasma-paracetamol concentrations are above the high-risk treatment line.
6. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified release preparations of paracetamol.

Those, whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least ninety six hours.

Chlorphenamine maleate

Central excitatory effects constitute the greatest danger in overdose.

Overdosage with **PARAGRIP C** may result in anticholinergic effects(paradoxical excitement, hallucinations, ataxia, unsteadiness, severe drowsiness, severe dryness of throat, nose and mouth, redness of face and shortness of breath and athetosis, urinary retention, dry mouth and fever). Fixed dilated pupils with a flushed face, convulsions, sinus tachycardia and cardiac dysrhythmias may occur. Overdosage may be fatal, especially in infants and children in whom the main symptoms are central nervous system stimulation and antimuscarinic effects. Deepening coma, cardiorespiratory collapse and death may occur within 18 hours. In adults, the usual symptoms are of central nervous system depression with drowsiness, coma and

convulsions.

Hypotension may also occur. Elderly patients are more susceptible to the central nervous system depressant and hypotensive effects even at the therapeutic doses. Treatment is symptomatic and supportive.

The stomach should be emptied by emesis or lavage. There is no specific antidote and treatment is symptomatic and supportive. It may be necessary to treat extrapyramidal reactions with diphenhydramine. The patient must be taken to a doctor or hospital immediately as specialised treatment may be necessary.

IDENTIFICATION:

PARAGRIP C is a white or almost white, round, flat tablet. It produces a slightly opalescent, colourless solution with a citrus flavour once dissolved in a glass of water.

PRESENTATION:

PARAGRIP C is available in white polypropylene tubes closed with a low-density polyethylene cap. Each tube contains 10 or 12 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25°C in a dry place. Keep the tube tightly closed.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

A39/5.8/0450

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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