PROFESSIONAL INFORMATION

SCHEDULING STATUS **S2**

1. NAME OF THE MEDICINE
RHINELEVE EFFERVESCENT TABLETS.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each effervescent tablet contains: 2 mg Chlorphenamine maleate, 500 mg Paracetamol and Sodium ascorbate equivalent to 250 mg Vitamin C.
RHINELEVE contains aspartame and sorbitol.

3. PHARMACEUTICAL FORM
White, to almost white, round, flat effervescent tablets with slight orange flavour.

4. CLINICAL PARTICULARS
Therapeutic indications
RHINELEVE is indicated for symptomatic relief of a sore throat, runny nose, sneezing, headache and generalised aching due to colds and flu.

Posology and method of administration
Posology
Adults and children over 12 years:
Take one tablet every 8 hours if necessary.

DO NOT EXCEED THE RECOMMENDED DOSE.
Do not use **RHINELEVE** continuously for more than 10 days without consulting your doctor.

Paediatric population
RHINELEVE is contraindicated in children aged 0 to 12 years (see section 4.3).

Method of administration
Dissolve one tablet in a glass of water and drink the contents immediately once the whole tablet has dissolved.

Contraindications
RHINELEVE is contraindicated in:
Hypersensitivity to the active substances or to any of the excipients (see section 6.1).
Severe liver function impairment.
Epilepsy.
Children under the age of 12 years.
Pregnancy and lactation

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

Special warnings and precautions for use
RHINELEVE 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.
Chlorphenamine, as in **RHINELEVE** 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. Should be used with care in patients with pyloroduodenal obstruction, epilepsy and severe cardiovascular disorders.
Doses of **RHINELEVE** in excess of those recommended may cause severe liver damage.
Consult a medical practitioner if pain or fever persist or gets worse at the recommended dosage or if new symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition.
Paediatric population

Store in a safe place out of reach of children.
Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities of **RHINELEVE**.
Use with caution in renal disease.
Ascorbic acid should be given with caution to patients with G6PD deficiency, as large doses can cause haemolysis. Ascorbic acid should be given with caution to patients with hyperoxaluria. As large doses may result in the formation of renal calcium oxalate calculi.
Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Caution is therefore required in patients with phenylketonuria (PKU). Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.
Patients with the rare hereditary condition of sorbitol intolerance should not take **RHINELEVE**.

Interaction with other medicines and other forms of interaction
No interaction studies have been performed.

Chlorphenamine:
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, guanethine, reserpine, methyldopa or 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.

Paracetamol:
Hepatotoxic medicines – Increased risk of hepatotoxicity.
Enzyme inducing medicines – increased risk of hepatotoxicity.
Possible decrease in therapeutic effects of **RHINELEVE**.
Metoclopramide – absorption of **RHINELEVE** may be accelerated.
Cholestyramine – absorption of **RHINELEVE** is reduced if given within one hour of cholestyramine.
Prolonged concurrent use of **RHINELEVE** with salicylates increases the risk of adverse renal effects.
Excretion may be affected and plasma concentrations
altered when given with probenecid.

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.

Fertility, pregnancy and lactation
Pregnancy
The safety of this medicine in pregnancy has not been established.

Breastfeeding
The safety of this medicine in lactating women has not been established.

Fertility
No fertility data is available.

Effects on ability to drive and use machines
RHINELEVE may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.
RHINELEVE 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.

Undesirable effects
Tabulated summary of adverse reactions
Chlorphenamine maleate:

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorder	Less frequent	Anaphylaxis including tightness of the chest and hypersensitivity reactions (including bronchospasm, angioedema)
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Drowsiness.
	Less frequent	Convulsions or seizures, dizziness, increased sweating, abnormal coordination, tremor, lassitude, euphoria, nervousness, insomnia, headache, sedation.
	Frequency unknown	Confusion, hallucinations, paraesthesias, ataxia
Eye disorders	Less frequent	Blurred vision, diplopia.
Ear and labyrinth disorders	Less frequent	Tinnitus.
Cardiac disorders	Less frequent	Palpitations, dysrhythmia and tachycardia.
	Frequency unknown	Tightness of the chest, tingling, heaviness and weakness of the hands.
Vascular disorders	Less frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Thickening of mucous
	Frequency unknown	Dryness of respiratory passages
Gastrointestinal disorders	Frequent	Dryness of mouth, nose or throat, gastrointestinal upset, loss of appetite, constipation, diarrhoea, nausea, vomiting.
	Frequency unknown	Epigastric pain, gastric reflux
Hepato-biliary disorders	Less frequent	Cholestasis, hepatitis or other hepatic function abnormalities.
Skin and subcutaneous tissue disorders	Less frequent	Exfoliative dermatitis, rashes.
	Frequency unknown	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	Difficult or painful urination, dysuria.
General disorders and administrative site conditions	Less frequent	Oedema, fatigue.

Paracetamol:

MedDRA system organ class	Frequency	Adverse reactions
Blood and the lymphatic system disorders	Less frequent	Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia and anaemia.
Hepato-biliary disorders	Less frequent	Hepatitis.
	Frequency unknown	Pancreatitis
Skin and subcutaneous tissue disorders	Less frequent	Allergic dermatitis.
Renal and urinary disorders	Less frequent	Renal colic, renal failure and sterile pyuria.
General disorders and administrative site conditions	Frequency unknown	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.

Sodium Ascorbate (Vitamin C):

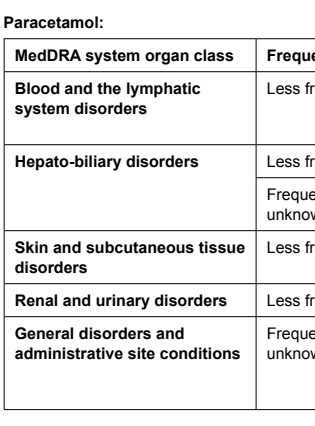
MedDRA system organ class	Frequency	Adverse reactions
Blood and the lymphatic system disorders	Frequency unknown	Ascorbic acid in large doses may also result in haemolysis in patients with glucose – 6 – phosphate dehydrogenase deficiency.
Gastrointestinal disorders	Frequency unknown	Large doses are reported to cause diarrhoea and other gastrointestinal disturbances.
Renal and urinary disorders	Frequency unknown	Large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi. Tolerance may be included with prolonged use of large doses

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

Overdose
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 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 overdosage 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 for paracetamol overdosage
Although evidence is limited, it is recommended that any adult person who has ingested 5 to 10 grams or more of paracetamol (or child who has had more than 140 mg / kg body weight) within the preceding four hours, should have stomach
emptied (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 administered 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 administered 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, may be misleading. Patients at risk of liver damage and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below.

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



1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentration drawn before four 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 drugs or with malnutrition or a history of alcohol abuse should be treated if the 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 **RHINELEVE** 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). Convulsions, tachycardia and cardiac arrhythmias 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 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.

5. PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
A.5.8 Preparations for the common cold including nasal decongestants.
RHINELEVE has analgesic, antipyretic and antihistaminic properties.

Pharmacokinetic properties
Chlorphenamine maleate:
Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract. Peak plasma concentrations occurs about 2,5 to 6 hours after oral administration and the effects usually last 4-6 hours.
Chlorphenamine appears to undergo considerable first-pass metabolism. Unchanged chlorphenamine and the metabolites are excreted mainly in the urine. Excretion is dependent on the urinary pH and flow rate.
About 70% of the 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:
Pharmacokinetics:
Paracetamol is well absorbed after oral administration. Peak plasma concentrations are reached 0,5 to 1,0 hours after administration. The plasma half
life is about 2 hours.
Plasma protein binding varies. 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%) and cysteine (about 3%). Paracetamol is mainly excreted renally as conjugated metabolites. 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:
Pharmacokinetics:
Sodium ascorbate is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissue.
The plasma concentrations of ascorbic acid rise as the dose ingested are increased until a plateau is reached with doses of about 90 to 150 mg daily. Excess of the body's needs is rapidly eliminated in the urine. Ascorbic acid crosses the placenta and is distributed into breast milk.

6. PHARMACEUTICAL PARTICULARS
List of excipients
Aspartame
Citric acid anhydrous
Lemon flavour
Orange flavour
Povidone K30
Simethicone emulsion
Sodium carbonate anhydrous
Sorbitol

Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

Shelf life
36 months

Special precautions for storage
Store at or below 25 ºC in a dry place.
Protect from light.
Keep the tube tightly closed.
KEEP OUT OF REACH OF CHILDREN

Nature and contents of container
10, 12, 20 Effervescent tablets packed in a Polypropropylene tube with polyethylene stoppers filled with silica gel.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd
106 16th Road, Building 2,
Midrand,
1686, South Africa

8. REGISTRATION NUMBER(S)
49/5.8/0944

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT