PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

EFFERFLU C COLD & FLU Effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains paracetamol 500 mg, sodium ascorbate equivalent to vitamin C 250 mg and chlorphenamine maleate 2 mg.

EFFERFLU C COLD & FLU contains 21,10 mg sorbitol per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Effervescent tablet.

EFFERFLU C COLD & FLU 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over 12 years:

One tablet every 8 hours, if necessary.

Consult a doctor if no relief is obtained from the recommended dosage.

Do not use EFFERFLU C COLD & FLU for more than 7 days without consulting a doctor.

Paediatric population

The safety and efficacy of EFFERFLU C COLD & FLU in children under the age of 12 years has not been established (see section 4.3).

Method of administration

Dissolve one tablet in a glass of water and drink the contents as soon as the whole tablet has dissolved.

Missed dose

Doctors should advise patients who forget to take EFFERFLU C COLD & FLU to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

EFFERFLU C COLD & FLU is contraindicated in:

- Hypersensitivity to paracetamol, sodium ascorbate, chlorphenamine maleate or to any of the ingredients of EFFERFLU C COLD & FLU.
- Severe liver function impairment.
- Coronary disease and cardiovascular disease such as ischaemic heart disease, dysrhythmia or tachycardia.
- Epilepsy.
- Children under the age of 12 years.
- Prior sensitivity to any antihistamine.
- Patients receiving monoamine oxidase inhibitor treatment, or within 14 days of stopping such treatment should not take EFFERFLU C COLD & FLU
- Patients undergoing anaesthesia with halothane or other halogenated anaesthetics, as they may induce ventricular fibrillation.

Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Chlorphenamine maleate:

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.

EFFERFLU C COLD & FLU may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.
EFFERFLU C COLD & FLU may enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics.

Chlorphenamine may suppress positive skin test results and should be stopped several days before the test.

Paracetamol:

Dosages of EFFERFLU C COLD & FLU 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 dosage, if new symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition.
Do not use EFFERFLU C COLD & FLU continuously for more than 7 days without consulting your doctor.

EFFERFLU C COLD & FLU 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.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities of EFFERFLU C COLD & FLU. Use with caution in renal disease.

Severe cutaneous adverse reactions (SCAR):

Severe cutaneous adverse reactions (SCAR) such as toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), drug induced hypersensitivity syndrome (DIHS) and fixed dose eruptions (FDE) have been reported in patents treated with paracetamol containing medicines. If a patient develops serious cutaneous adverse reaction, treatment with EFFERFLU C COLD & FLU must immediately be discontinued and appropriate treatment instituted.

Excipients:

EFFERFLU C COLD & FLU contains the sugar alcohol, sorbitol.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Patients sensitive to another antihistamine may be sensitive to EFFERFLU C COLD & FLU (see section 4.3).

EFFERFLU C COLD & FLU may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants e.g. sedatives and tranquilizers (see section 4.2).

Paracetamol:

Hepatotoxic medicines – Increased risk of hepatotoxicity.
Enzyme inducing medicines – Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of EFFERFLU C COLD & FLU.
Metoclopramide – Absorption of EFFERFLU C COLD & FLU may be accelerated.
Cholestyramine – Absorption of EFFERFLU C COLD & FLU is reduced if given within one hour of cholestyramine. Prolonged concurrent use of EFFERFLU C COLD & FLU 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 and belladonna 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 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy in pregnancy has not been established (see section 4.3)

Breastfeeding

The safety and efficacy in lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

EFFERFLU C COLD & FLU 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions (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
Renal and urinary disorders	Less frequent	Renal colic, renal failure, 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.

Immune system disorders	Less frequent	Severe cutaneous adverse reactions that may manifest in drug induced hypersensitivity syndrome (DIHS)*, fixed drug eruptions (FDE)*, toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS).

*Post-Marketing Experience

Tabulated summary of adverse reactions (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 and 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, 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, 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, rashes 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 frequency
General disorders and administrative site conditions	Less frequent	Oedema, fatigue

Tabulated summary of adverse reactions (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-phosphate 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

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 Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 OVERDOSE

Paracetamol:

Signs and symptoms:

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 dysrhythmias have been reported.

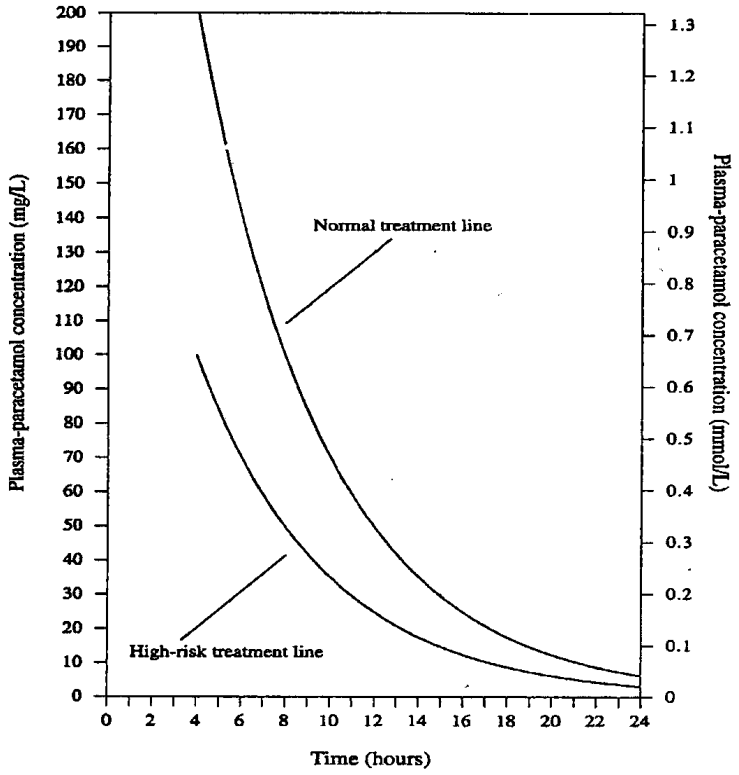
Management of overdose:

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 their 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 should be 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 determined 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. A linear plot of plasma paracetamol concentration against hours after ingestion:



1. The time co-ordinates 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:

Signs and symptoms:

Central excitatory effects constitute the greatest danger in overdose. Overdosage with EFFERFLU C COLD & FLU 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).

Fixed dilated pupils with a flushed face, convulsions, sinus 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 also occur. Elderly patients are more susceptible to the central nervous system depressant and hypotensive effects even at the therapeutic doses.

Management of overdose:

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.5.8. Preparations for the common cold, including nasal decongestants.

Mechanism of action

Paracetamol/chlorphenamine maleate/ascorbic acid effervescent tablets have analgesic, antipyretic and antihistaminic properties.

Chlorphenamine maleate:

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.

Paracetamol:

Paracetamol has analgesic and antipyretic effects.

Sodium ascorbate:

A vitamin supplement.

5.2 Pharmacokinetic properties

Chlorphenamine maleate:

Absorption:

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.

Distribution:

About 70 % ± 3 % of chlorphenamine in the circulation is bound to plasma proteins. Chlorphenamine is widely distributed in the body and enters the CNS. The half-life in adults is 20 ± 5 hours but elimination is much more rapid in children.

Biotransformation:

Bioavailability is low, values of 41 ± 16 % having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism.

Elimination:

Unchanged chlorphenamine and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate.

Paracetamol:

Absorption:

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0,5 to 1 hour.

Distribution:

The plasma half-life is about 2 hours. Plasma protein binding is variable. Paracetamol is relatively uniformly distributed throughout most body fluids.

Biotransformation:

Paracetamol is metabolised in the liver, primarily by conjugation with glucuronic acid (about 60 %), sulphuric acid (about 35 %) and cysteine (about 3 %); small amounts of hydroxylated and deacetylated metabolites also have been detected.

Elimination:

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:

Absorption:

Sodium ascorbate is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissue.

Distribution:

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.

Biotransformation:

Ascorbic acid crosses the placenta and is distributed into breast milk.

Elimination:

Excess of the body's needs is rapidly eliminated unchanged in the urine.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid

Aspartame

Lemon flavour

Orange flavour

Povidone K30

Simethicone

Sodium carbonate anhydrous

Sodium hydrogen carbonate

Sorbitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

EFFERFLU C COLD & FLU is available in white polypropylene tubes closed with a low-density polyethylene cap. Each tube contains 10, 12 or 20 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

RSA S2 A39/5.8/0451

9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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