PROFESSIONAL INFORMATION

EFFERFLU C COLD & FLU

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 sugar alcohol, sorbitol 212 mg per tablet.

EFFERFLU C COLD & FLU contains aspartame 40 mg.

EFFERFLU C COLD & FLU contains 314 mg of sodium per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablets.

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

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over 12 years:

One tablet every 8 hours, if necessary.

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

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

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

Medical practitioners 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 the following patients:

- hypersensitivity to paracetamol, sodium ascorbate, chlorphenamine maleate or to any of the excipients of EFFERFLU C COLD & FLU (see section 6.1)
- 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 (MAOI) treatment, or within 14 days of stopping such treatment should not take EFFERFLU C COLD & FLU, as the anticholinergic properties of chlorphenamine are intensified by MAOIs (see sections 4.3 and 4.5)
- patients undergoing anaesthesia with halothane or other halogenated anaesthetics, as they may induce ventricular fibrillation
- patients having acute attacks of asthma.

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

4.4 Special warnings and precautions for use

Chlorphenamine maleate:

Chlorphenamine maleate may produce epileptiform seizures in patients with focal lesions of the cerebral cortex. Allergic reactions and cross-sensitivity to related medicines may be produced.

Should be used with caution in patients with prostatic hypertrophy, narrow angle glaucoma, emphysema, chronic bronchitis, porphyria or urinary retention. Paradoxical hyper excitability, nervousness, insomnia, tachycardia, tremors and convulsions 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, severe cardiovascular disorders, bronchiectasis and asthma, hepatic impairment and renal impairment.

Avoid use in elderly patients with confusion.

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:

Do not use with any other paracetamol-containing medicines.

The concomitant use with other medicines containing paracetamol may lead to an overdose.

Dosages of EFFERFLU C COLD & FLU in excess of those recommended may cause severe liver damage which may require liver transplant or lead to death. 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.

Underlying liver disease increases the risk of paracetamol-related liver damage.

Do not use EFFERFLU C COLD & FLU continuously for more than 7 days without consulting your medical practitioner.

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 medical practitioner, 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.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index, are chronic heavy users of alcohol, have alcohol induced dehydration or have sepsis.

In patients with glutathione depleted states and in concomitant administration with flucloxacillin, as the use of paracetamol may increase the risk of metabolic acidosis.

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 patients 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 with known effect:

Sorbitol

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

Patients with rare hereditary problems of fructose intolerance (HFI) should not take this medicinal product.

Aspartame

This medicine contains aspartame 40 mg.

Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine.

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Sodium

EFFERFLU C COLD & FLU contains 314 mg sodium per effervescent tablet, equivalent to 15,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 such as carbamazepine, phenytoin, phenobarbital, rifampicin and St John's wort (*Hypericum perforatum*) – increased risk of hepatotoxicity. Possible decrease in therapeutic effects of EFFERFLU C COLD & FLU.

Metoclopramide or domperidone – 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.

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.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

Isoniazid affects the pharmacokinetics of paracetamol with possible potentiation of liver toxicity.

Interference with laboratory tests:

Paracetamol may affect uric acid tests by wolframato phosphoric acid, and blood sugar tests by glucose-oxidase peroxidase.

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 central nervous system (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.
Antihistamines may suppress positive skin test results and should be stopped several days before the test.

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).

Fertility

There is no data on fertility with EFFERFLU C COLD & FLU.

4.7 Effects on ability to drive and use machines

EFFERFLU C COLD & FLU may lead to drowsiness, dizziness, blurred vision 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

The incidence of adverse reactions tends to increase with increasing dose.

The frequencies of adverse events are ranked according to the following:

Frequent = (≥ 1/100 to < 1/10).

Less frequent = Infrequent (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000).

Frequency not known = cannot be estimated from the available data.

Tabulated list of adverse effects (paracetamol)

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia and anaemia, platelet disorders, stem cell disorders, methaemoglobenaemia

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), anaphylaxis
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia
Psychiatric disorders	Less frequent	Depression, confusion, hallucinations
Nervous system disorders	Less frequent	Tremor, headache
Eye disorders	Less frequent	Abnormal vision
Cardiac disorders	Less frequent	Oedema
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm in patients' sensitive to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
Gastrointestinal disorders	Less frequent	Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting

Hepatobiliary disorders	Less frequent Frequency unknown	Hepatitis, abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice Pancreatitis, hepatotoxicity
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Allergic dermatitis, pruritus, rash, sweating, purpura, angioedema, urticaria Dermatitis
Renal and urinary disorders	Less frequent	Renal colic, renal failure, sterile pyuria
General disorders and administrative site conditions	Less frequent Frequency unknown	Dizziness (excluding vertigo), malaise, pyrexia, sedation 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
Injury and poisoning	Less frequent	Overdose and poisoning

*Post-Marketing Experience

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

Tabulated summary of adverse reactions (chlorphenamine maleate):

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequency unknown	Allergic reaction, angioedema, anaphylactic reactions
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)
Metabolism and nutrition disorders	Frequency unknown	Anorexia
Psychiatric disorders	Frequency unknown	Depression, confusion*, excitation*, irritability*, nightmares*
Nervous system disorders	Frequent	Drowsiness, central nervous system reactions include sedation, convulsions or seizures, dizziness, increased sweating, abnormal coordination, tremor, lassitude, euphoria, nervousness, insomnia, headache, somnolence
	Frequency unknown	Confusion, hallucinations, paraesthesias and ataxia

Eye disorders	Less frequent	Blurred vision, diplopia
Ear and labyrinth disorders	Frequency unknown	Tinnitus
Cardiac disorders	Less frequent Frequency unknown	Palpitations, dysrhythmia and tachycardia Hypertension, tightness of the chest, tingling, heaviness and weakness of the hands
Vascular disorders	Frequency unknown	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Thickening of mucous Dryness of the respiratory passages, tightness of chest
Gastrointestinal disorders	Frequent Frequency unknown	Dryness of mouth, nose or throat, gastrointestinal upset, loss of appetite, constipation, diarrhoea, nausea, vomiting Epigastric pain, gastric reflux
Hepatobiliary disorders	Less frequent	Cholestasis, hepatitis or other hepatic function abnormalities, including jaundice
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, muscular weakness
Renal and urinary disorders	Less frequent Frequency unknown	Difficult or painful urination, dysuria Urinary frequency, urinary retention
General disorders and administrative site conditions	Less frequent	Oedema, fatigue, chest tightness

*Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g., increased energy, restlessness, nervousness).

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 gastrointestinal 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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Paracetamol:

Signs and symptoms:

Prompt treatment is essential. In the event of an overdosage, consult a medical practitioner 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, acquired immunodeficiency syndrome (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 - 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:

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

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:

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 medical practitioner 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 - 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 - 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 % - 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 adults.

Pharmacokinetics in special patient groups

Renal impairment

In cases of severe renal insufficiency (creatinine clearance lower than 10 mL/min) the elimination of paracetamol and its metabolites is delayed.

Elderly

The capacity for conjugation is not modified.

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 - 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid

Aspartame

Lemon flavour

Orange flavour

Povidone

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 THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

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