1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

FLUSIN S EFFERVESCENT (effervescent tablet)

COMPOSITION

Each tablet of FLUSIN S EFFERVESCENT contains:

Pseudoephedrine hydrochloride	50 mg
Chlorphenamine maleate	4 mg
Paracetamol	500 mg
Vitamin C	330 mg

Excipients:

Aspartame, citric acid anhydrous, colloidal silicon dioxide, ginger flavour 77903-31, light liquid paraffin, polyethylene glycol, sodium bicarbonate, sodium carbonate anhydrous

Contains sweetener: Aspartame	60,0 mg

CATEGORY AND CLASS

A 5.8 Preparations for the common cold including nasal decongestants

PHARMACOLOGICAL ACTION

Pharmacodynamic 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.

Pseudoephedrine hydrochloride

Pseudoephedrine is a sympathomimetic vasoconstrictor with properties that can produce tachycardia, increased blood pressure, and CNS stimulation.

Paracetamol

Paracetamol has analgesic and antipyretic effects.

Pharmacokinetic properties

Chlorphenamine maleate

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract and peak plasma concentrations occur about 2,5 to 6 hours after oral doses and effects usually last 4 to 6 hours.

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

Pseudoephedrine hydrochloride

Pseudoephedrine is extensively absorbed and has an oral bioavailability of 100 % and a half-life of about 4,3 to 8 hours.

Paracetamol

Paracetamol is well absorbed after oral administration. Peak plasma concentrations occur within 30 to 60 minutes and the half-life in plasma is about 2 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding to plasma proteins is variable. Some 90 % to 100 % of the substance may be recovered in the urine within the first day at therapeutic dosing, primarily after hepatic 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.

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

Vitamin C

A vitamin supplement.

INDICATIONS

FLUSIN S EFFERVESCENT is indicated for:

- Symptomatic relief of minor aches and pains, and sinus and nasal congestion associated with colds and flu.

CONTRAINDICATIONS

FLUSIN S EFFERVESCENT is contrainidicated in:

- Patients with hypersensitivity to chlorphenamine maleate, paracetamol, pseudoephedrine hydrochloride and/or vitamin C or to any of the excipients in FLUSIN S EFFERVESCENT (see COMPOSITION).
- Coronary disease and cardiovascular disease such as ischaemic heart disease, dysrhythmia or tachycardia

- Children under the age of 12 years old.
- Patients sensitive to one antihistamine may be sensitive to others.
- Patients receiving monoamine oxidase inhibitor treatment, or within 14 days of stopping such treatment should not take FLUSIN S EFFERVESCENT.
- Severe liver function impairment.
- And should be avoided in 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 HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

FLUSIN S EFFERVESCENT contains aspartame. Aspartame should be avoided or its intake restricted in patients with phenylketonuria.

Chlorphenamine maleate

FLUSIN S EFFERVESCENT may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system

depressants. May enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics.

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.

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.

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

Pseudoephedrine hydrochloride

After 5 to 7 days tachyphylaxis may occur and the product loses effect. If symptoms do not improve, or are accompanied by a fever, consult a doctor.

Exceeding the recommended dosage may result in nervousness, dizziness, sleeplessness, tremulousness or cardiac dysrhythmia. This may also occur in sensitive individuals at small doses.

Should be used with caution in patients with hypertension, hyperthyroidism, diabetes mellitus, closed-angle glaucoma, prostatic hypertrophy, phaeochromocytoma, occlusive vascular disease including arteriosclerosis, aneurysms.

Anginal pains may be precipitated in patients with angina pectoris.

Paracetamol

FLUSIN S EFFERVESCENT should be stopped if fever persists or pain worsens.

FLUSIN S EFFERVESCENT contains paracetamol which may be fatal in overdose. 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 paracetamol.

Use with caution in renal disease.

Effects on ability to drive and use machines

FLUSIN S EFFERVESCENT 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 (see WARNINGS AND SPECIAL PRECAUTIONS).

INTERACTIONS

Patients sensitive to another antihistamine may be sensitive to FLUSIN S EFFERVESCENT (see CONTRAINDICATIONS).

FLUSIN S EFFERVESCENT 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 WARNINGS AND SPECIAL PRECAUTIONS).

Chlorphenamine

Chlorphenamine may increase the risk of phenytoin toxicity.

There may be an excessive anticholinergic effect caused by the combination of belladonna and chlorphenamine.

All sedatives, including alcohol, will potentiate depressant effects on the central nervous system if taken with antihistamines.

Medications tending to cause extrapyramidal reactions and those with anticholinergic effects may be potentiated. These include tricyclic antidepressants, maprotiline and monoamine oxidase inhibitors.

Pseudoephedrine

Pseudoephedrine may cause a hypertensive crisis in patients receiving a monoamine oxidase inhibitor (MAOI) (see CONTRAINDICATIONS).

FLUSIN S EFFERVESCENT should be avoided in patients undergoing anaesthesia with halothane or other halogenated anaesthetics as they may induce ventricular fibrillation (see CONTRAINDICATIONS).

Reversal of action of antihypertensive medicines may occur and therefore special care is advisable in patients receiving antihypertensive therapy. Interactions with alpha- and beta-blockers may be complex and can produce hypertensive crisis.

An increased risk of dysrhythmias may occur given to patients receiving cardiac glycosides, quinidine or tricyclic antidepressants.Interactions are possible with tricyclic antidepressants, guanethidine, reserpine, alpha-methyldopa and digoxin.

Should be avoided or used with caution in patients undergoing anaesthesia with halothane or other halogenated anaesthetics as they may induce ventricular fibrillation.

Aluminium hydroxide mixtures may enhance the absorption of pseudoephedrine.

Paracetamol

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines such as isoniazid or medicines that induce liver microsomal enzymes.

The absorption of paracetamol may be accelerated by medicines such as metoclopramide.

Excretion may be affected and plasma concentrations altered when given with probenecid.

Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Vitamin C

May interact with desferrioxamine, hormonal contraceptives, fluphenazine and warfarin.

HUMAN REPRODUCTION

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

DOSAGE AND DIRECTIONS FOR USE

Adults and children over 12 years of age:

One tablet every 6 hours if necessary.

Place one tablet in a glass of warm water and allow to dissolve. Drink the contents immediately once the whole tablet has dissolved.

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

Do not use this product for more than 7 days without consulting a doctor.

SIDE EFFECTS

Paracetamol

Blood and the lymphatic system disorders

Less frequent: The use of paracetamol has been associated with the occurrence of agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, leukopenia, anaemia

Hepato-biliary disorders

Less frequent: Hepatitis

Frequency unknown: Pancreatitis

Skin and subcutaneous tissue disorders

Less frequent: Skin rashes and other allergic reactions. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions

Frequency Unknown: Dermatitis

Renal and urinary disorders

Frequency unknown: Renal colic, renal failure and sterile pyuria

Pseudoephedrine hydrochloride

Metabolism and nutrition disorders

Frequency unknown: Altered metabolism, including disturbances of glucose metabolism

Psychiatric disorders

Frequent: Anxiety, restlessness, insomnia

Less frequent: Tremor, weakness and psychotic states

Frequency unknown: Fear, confusion, irritability

Nervous system disorders

Less frequent: Headache

Cardiac disorders

Less frequent: Hypotension with dizziness and fainting and flushing may occur. Stimulation of B_1-adrenergic receptors of the heart may produce tachycardia and cardiac dysrhythmias, palpitations and cardiac arrest. There may be reflex bradycardia

Frequency unknown: Vasoconstriction with resultant hypertension. The rise in blood pressure may produce cerebral haemorrhage and pulmonary oedema

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea

Gastrointestinal disorders

Less frequent: Nausea and vomiting

Frequency unknown: Appetite may be reduced

Skin and subcutaneous tissue disorders

Less frequent: Sweating

Frequency unknown: Hypersalivation

Renal and urinary disorders

Less frequent: Difficulty in maturation and urinary retention

Chlorphenamine maleate

Blood and lymphatic system disorders

Less frequent: Blood dyscrasias, including agranulocytosis, leukopenia, haemolytic anaemia and thrombocytopenia

Psychiatric disorders

Frequency unknown: Depression

Nervous system disorders

Less frequent: Central nervous system reactions include sedation, drowsiness, dizziness, fatigue, tremors and incoordination

Frequency unknown: Confusion, hallucinations, convulsions, headache, tinnitus, lassitude, nervousness, insomnia , paraesthesias, ataxia, blurred vision

Cardiac disorders

Less frequent: Palpitation and dysrhythmias, tachycardia

Frequency unknown: Hypertension, hypotension, headache, tightness of the chest, tingling, heaviness and weakness of the hands

Respiratory, thoracic and mediastinal disorders

Less frequent: Thickening of mucous

Frequency unknown: Dryness of the respiratory passages

Gastrointestinal disorders

Less frequent: Loss of appetite, reduction in tone and motility of the gastrointestinal tract, resulting in constipation

Frequency unknown: Nausea, vomiting, epigastric pain and gastric reflux have occurred, diarrhoea and dryness of the mouth and throat

Skin and subcutaneous tissue disorders

Less frequent: May cause rashes and hypersensitivity reactions (including bronchospasm, angioedema and anaphylaxis)

Frequency unknown: Photosensitivity and skin rash, allergic dermatitis, drug fever, hair loss and sweating

Musculoskeletal disorders

Frequency unknown: Extrapyramidal effects with muscle spasms and dystonia, myalgia

Renal and urinary disorders

Less frequent: Urinary retention, dysuria

Frequency unknown: Urinary frequency

Vitamin C

Blood and the lymphatic system disorders

Frequency unknown: Large doses of vitamin C have resulted in haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency

Gastrointestinal disorders

Less frequent: Large doses are reported to cause diarrhoea and other gastrointestinal disturbances

Renal and urinary disorders

Frequency unknown: Associated with the formation of renal calcium oxalate calculi. Ascorbic acid 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 TREATMENTS

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. 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 to10 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 carbamazapine.

Symptoms of paracetamol overdosage in the first 24 hours are 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/INR. 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.

Treatment of paracetamol overdosage:

Prompt treatment is essential in the management of paracetamol overdosage. Any adult person who has ingested 5 to 10 g or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding 4 hours, should have the 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 intubation should precede gastric lavage in order to avoid aspiration.

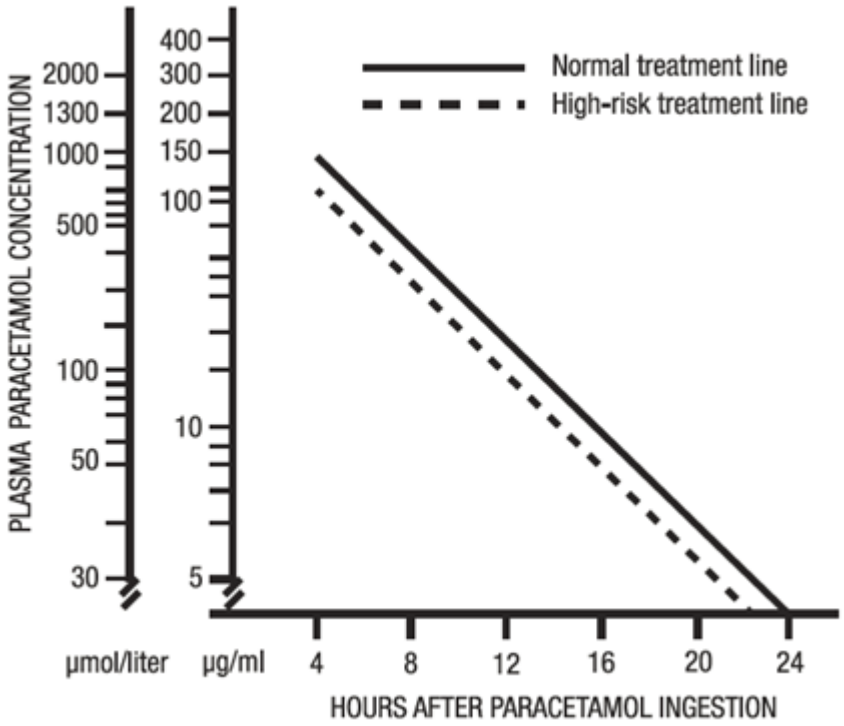
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml of dextrose injection over the next 4 hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next 16 hours.

The volume of intravenous fluids should be modified for children.

Orally (not the treatment of choice): 140 mg/kg as a 5 % solution initially, followed by a 70 mg/kg solution every 4 hours for 17 doses. N-acetylcysteine is more likely to be effective if administered within 8 hours of overdosage.

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



Those whose plasma paracetamol levels are above the “Normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg 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 time/INR 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. Symptoms include drowsiness or paradoxical excitement, hallucinations, ataxia, incoordination, athetosis and convulsions. Fixed dilated pupils with a flushed face, sinus tachycardia, dyspnoea, urinary retention, dry mouth and fever. Terminally deepening coma and cardio-respiratory collapse.

Children and the elderly are more likely to exhibit anticholinergic and central nervous system stimulant effects. The elderly are prone to hypotension.

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.

Pseudoephedrine hydrochloride

Pseudoephedrine overdosage produces central nervous system stimulation with excitement, restlessness, rapid speech, hallucinations, hypertonicity and hyperflexia with dilated pupils and tachycardia.Beta-blockers may be administered for tachycardia.

Potassium supplements may be required.

IDENTIFICATION

Round biplane tablet, off-white with a pink tinge and a rough surface, with clean edges and a sweet ginger smell. Produces a slightly pink, clear solution a sweet ginger taste.

PRESENTATION

12 tablets are packed in aluminium tubes, seamless with lacquered inner and outer surfaces with a low density polyethylene press-on white cap with a spiral tablet stabilizer, with drier cavity with self indicating silica gel drier and then packed in an outer cardboard carton.

STORAGE INSTRUCTIONS

Store in a cool place at or below 25 °C.

Keep tube tightly closed.

Keep in original packaging until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

30/5.8/0001

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

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