1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

FLUSIN S EFFERVESCENT 50 mg/ 4 mg/ 500 mg/ 330 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of FLUSIN S EFFERVESCENT contains 50 mg pseudoephedrine hydrochloride, 4 mg chlorphenamine maleate, 500 mg paracetamol and 330 mg vitamin C.

Contains sweetener: Aspartame 60,0 mg

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablet

FLUSIN S EFFERVESCENT is a 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 with a ginger taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

FLUSIN S EFFERVESCENT is indicated for:

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

4.2. Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over 12 years of age:

One tablet every 6 hours if necessary.

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.

Paediatric population

The safety and efficacy of FLUSIN S EFFERVESCENT in children under 12 years has not been established (see section 4.3).

Method of administration

For oral administration.

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

4.3. Contraindications

FLUSIN S EFFERVESCENT is contraindicated in:

- Patients with hypersensitivity to chlorphenamine maleate, paracetamol, pseudoephedrine hydrochloride, vitamin C or to any of the excipients in FLUSIN S EFFERVESCENT (see section 2 and 6.1).
- Coronary disease and cardiovascular disease including angina, ischaemic heart disease, peripheral vascular 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 (MAOI), or within 14 days of stopping such treatment should not take FLUSIN S EFFERVESCENT (see section 4.4).
- Severe liver function impairment.
- Paracetamol should not be used in patients with severe renal disease.
- FLUSIN S EFFERVESCENT 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 section 4.6).
- Patients suffering from hypertension, hyperthyroidism, phaeochromocytoma, closed angle glaucoma or where intraocular pressure is raised and diabetes mellitus.
- Patients with hyperoxaluria.
- Patients taking beta-blockers (see section 4.5).

4.4. Special warnings and precautions for use

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.

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. Caution should be used when driving a motor vehicle or operating machinery or performing potentially dangerous tasks, where loss of concentration may lead to accidents.

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, tranquilisers and antipsychotics.

The anticholinergic properties of chlorphenamine maleate as contained in FLUSIN S EFFERVESCENT may cause drowsiness, dizziness, blurred vision and psychomotor impairment. 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.

FLUSIN S EFFERVESCENT should be used with caution in patients with prostatic hypertrophy, emphysema or chronic bronchitis, porphyria, patients with bronchial asthma or where cough is accompanied by excessive secretions should be advised to consult a doctor before taking this medicine.

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. The warning signs of damage caused by ototoxic medicines may be masked by chlorphenamine.

FLUSIN S EFFERVESCENT should be used with care in patients with pyloroduodenal obstruction and epilepsy.

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

FLUSIN S EFFERVESCENT should not be taken concurrently with medicines that cause sedation such as anxiolytics and hypnotics as these may increase the sedative effects.

Other antihistamine containing medicines, including antihistamine containing cough and cold medicines should not be taken concurrently with FLUSIN S EFFERVESCENT.

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 (see section 4.2).

Should be used with caution in patients with difficulty in urination, prostatic hypertrophy and aneurysms.

Anginal pains may be precipitated in patients with angina pectoris (see section 4.3).

Acute Generalised exanthematous pustulosis (AGEP)

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) have been reported with pseudoephedrine-containing medicines, such as FLUSIN S EFFERVESCENT. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, body, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as formation of small pustules occur, with or without pyrexia or erythema, then treatment with pseudoephedrine should be discontinued and a doctor should be consulted.

Ischaemic colitis

FLUSIN S EFFERVESCENT should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop

Ischaemic optic neuropathy

Cases of ischaemic optic neuropathy have been reported with pseudoephedrine hydrochloride as contained in FLUSIN S EFFERVESCENT.

FLUSIN S EFFERVESCENT should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Posterior reversible encephalopathy syndrome (PRES) and Reversible cerebral vasoconstriction syndrome (RCVS)

FLUSIN S EFFERVESCENT should not be used in patients with severe or uncontrolled high blood pressure, or with severe acute or chronic kidney disease/failure. Patients should be advised to stop using these medicines immediately and seek treatment if they develop symptoms of PRES or RCVS which may include visual disturbance, seizure, headaches, and altered mentation.

Paracetamol

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

Dosages in excess of those recommended may cause severe liver or kidney damage. Patients with impaired kidney or liver function should take paracetamol under medical supervision only.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take paracetamol (see section 4.3).

Severe Cutaneous Adverse Reactions (SCARS)

Severe Cutaneous Adverse Reactions (SCARS) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol

containing medicines. If a patient develops SCAR, treatment with FLUSIN S EFFERVESCENT must immediately be discontinued and appropriate treatment instituted.

Patients should be informed about the signs of serious skin reactions and the use of FLUSIN S EFFERVESCENT should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Consult your doctor if pain or fever persists or gets worse, if new symptoms occur or if redness and swelling is present, as these could be signs of a serious condition.

Do not use FLUSIN S EFFERVESCENT with any other medicines containing paracetamol.

High Anion gap metabolic acidosis (HAGMA)

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Ascorbic acid

Tolerance may be induced in patients taking high doses of ascorbic acid, as contained in FLUSIN S EFFERVESCENT.

Increased intake of ascorbic acid over a prolonged period may result in increased renal clearance of ascorbic acid, and deficiency may result if the intake is reduced or withdrawn rapidly (see section 4.8).

Interference with serological testing

Ascorbic acid may interfere with tests and assays for urinary glucose, giving false-negative results with methods utilising glucose oxidase with indicator (e.g. Labstix, Testape) and false- positive results with neocuproin methods.

Estimation of uric acid by phosphotungstate or uricase with copper reduction and measurement of creatinine in non-deproteinised serum may also be affected.

High doses of ascorbic acid may give false-negative readings in faecal occult blood tests.

Excipients

FLUSIN S EFFERVESCENT contains aspartame.

Aspartame should be avoided, or its intake restricted in patients with phenylketonuria.

4.5. Interaction with other medicines and other forms of interaction

Patients sensitive to another antihistamine may be sensitive to FLUSIN S EFFERVESCENT (see section 4.3).

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 section 4.4).

Combinations containing any of the following medicines, depending on the amount, may also interact with FLUSIN S EFFERVESCENT.

Chlorphenamine

Phenytoin: Chlorphenamine may increase the risk of phenytoin toxicity.

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

Sedatives: All sedatives (barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics), 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

MAOIs: Pseudoephedrine may cause a hypertensive crisis and prolong and intensify the cardiac stimulant and vasopressor effects in patients receiving a monoamine oxidase inhibitor (MAOI) (see section 4.3). FLUSIN S EFFERVESCENT should not be administered during or within 14 days following the administration of a MAOI.

Anaesthetics: FLUSIN S EFFERVESCENT should be avoided in patients undergoing anaesthesia with halothane or other halogenated anaesthetics as they may induce ventricular fibrillation (see section 4.3).

Cardiovascular medicines: Pseudoephedrine as contained in FLUSIN S EFFERVESCENT may reverse the action of cardiovascular medicines and therefore special care is advisable in patients receiving such therapy.

Antihypertensives: Reversal of the action of antihypertensive medicines may occur. 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.

Aluminium hydroxide mixtures: May enhance the absorption rate of pseudoephedrine.

CNS stimulants: May result in additive CNS stimulation to excessive levels, which may cause unwanted effects, such as nervousness, irritability, insomnia, or possibly convulsions or cardiac dysrhythmias.

Doxapram: Used concurrently with FLUSIN S EFFERVESCENT may increase the pressor effects of either doxapram or sympathomimetic amines.

Ergot alkaloids (ergotamine & methysergide): May lead to an increased risk of ergotism.

Appetite suppressants and amphetamine-like psychostimulants: May lead to an increased risk of hypertension.

Oxytocin: May lead to an increased risk of hypertension.

Paracetamol

Isoniazid: 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.

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

Probenecid: 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.

NSAIDs: Prolonged concurrent use of paracetamol with other NSAIDs may also increase the risk of adverse renal effects.

Zidovudine: Paracetamol may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine; zidovudine may also inhibit the hepatic glucuronidation of paracetamol.

Warfarin: Paracetamol can potentiate the anticoagulant effects of warfarin and other coumarin derivatives. Patients should consult a doctor or pharmacist before use if they are taking warfarin or other coumarin derivatives.

Flucloxacillin: Caution should be taken when FLUSIN S EFFERVESCENT is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4).

Anticonvulsants and oral contraceptive steroids: May increase the rate at which paracetamol is metabolised, leading to a reduced plasma concentrations.

Ascorbic acid

May interact with fluphenazine and warfarin.

Amphetamine: Ascorbic acid increases the renal excretion of amphetamine.

Smoking and Oral contraceptives: The plasma concentration of ascorbate is decreased by smoking and oral contraceptives.

Iron: Ascorbic acid increases the absorption of iron.

Aspirin: Concomitant administration of aspirin and ascorbic acid may interfere with absorption of ascorbic acid. Renal excretion of salicylate is not affected and does not lead to reduced anti-inflammatory effects of aspirin.

Antacids: Concomitant administration of aluminium-containing antacids may increase urinary aluminium elimination. Concurrent administration of antacids and ascorbic acid is not recommended, especially in patients with renal insufficiency.

Amygdalin: Co-administration with amygdalin (a complementary medicine) can cause cyanide toxicity.

Desferrioxamine: Concurrent administration of ascorbic acid with desferrioxamine enhances urinary iron excretion. Cases of cardiomyopathy and congestive heart failure have been reported in patients with idiopathic haemochromatosis and thalassaemias receiving desferrioxamine who were subsequently given ascorbic acid. Ascorbic acid should be used with caution in these patients and cardiac function monitored.

Ascorbic acid may interfere with biochemical determinations of creatinine, uric acid and glucose in samples of blood and urine.

4.6. Fertility, pregnancy and lactation

The use of FLUSIN S EFFERVESCENT is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

The safety of FLUSIN S EFFERVESCENT during pregnancy has not been established.

Breastfeeding

The safety of FLUSIN S EFFERVESCENT during breastfeeding has not been established.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

FLUSIN S EFFERVESCENT 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 (see section 4.4).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

Paracetamol

System organ class	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders	Agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, leucopenia, anaemia	
Immune system disorders	Sensitivity/allergic reactions resulting in skin rash, laryngeal oedema, angioedema and anaphylaxis	
Metabolism and nutrition disorders		Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Gastrointestinal disorders	Mucosal lesions, pancreatitis	
Hepatobiliary disorders	Hepatitis	

Skin and subcutaneous tissue disorders	Skin rashes, other allergic reactions, erythematous*, urticarial rash*	Dermatitis, Severe Cutaneous Adverse Reactions (SCARS) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE), dermatitis
Renal and urinary disorders		Renal colic, renal failure, sterile pyuria
General disorders and administrative site conditions	Fever	

* The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions

Pseudoephedrine hydrochloride

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity reactions, including cross-sensitivity that may occur with other sympathomimetics
Metabolism and nutrition disorders		Decreased appetite, hypokalaemia, altered metabolism	Disturbances of glucose metabolism
Psychiatric disorders	Anxiety, restlessness, insomnia,		

	fear, confusion, irritability, psychotic states		
Nervous system disorders	Tremor, dizziness,	Headache, cerebral haemorrhage,	Excitability, hallucinations, paranoid delusions, posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS)
Eye disorders			Ischaemic optic neuropathy
Cardiac disorders		Pulmonary oedema, cardiac dysrhythmias, anginal pain, palpitations, and cardiac arrest	Vasocconstriction with resultant hypertension
Vascular disorders		Hypertension, reflex bradycardia, tachycardia, hypotension, fainting	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	
Gastrointestinal disorders		Nausea, vomiting, hypersalivation	Reduced appetite,
			ischaemic colitis
Skin and subcutaneous tissue disorders			Skin reactions including rash, severe skin reactions, including acute generalized exanthematous pustulosis (AGEP)
Renal and urinary disorders		Difficulty in micturition, urinary retention	

General disorders and administrative site conditions	Weakness, sweating, tolerance with dependence		
Investigations		Changes in blood sugar levels	

Chlorphenamine maleate

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Blood dyscrasias, including agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia	
Immune system disorders		Hypersensitivity reactions such as pruritus or rash,	Allergic dermatitis, drug fever
		bronchospasm, angioedema, anaphylaxis	
Metabolism and nutrition disorders			Anorexia
Psychiatric disorders		Nervousness, euphoria, irritability*, nightmares*, hallucinations	Depression,
			excitation*
Nervous system disorders	Sedation, varying from slight drowsiness to deep sleep (somnolence), including lassitude, dizziness and incoordination	CNS reactions including fatigue, tremors	Confusion, tinnitus, ataxia,
		insomnia, convulsions, headache, paraesthesias	tingling, heaviness and weakness of the hands

		extrapyramidal effects	
Eye disorders	Blurred vision		
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders		Palpitation and dysrhythmias, tachycardia	
Vascular disorders		Hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders		Thickening of mucous,	Dryness of the respiratory passages
		tightness of the chest	
Gastrointestinal disorders	Nausea, dry mouth	Loss of appetite, reduction in tone and motility of the gastrointestinal tract resulting in constipation,	Dry throat
		gastric reflux, diarrhoea, epigastric pain, vomiting, dyspepsia	
Hepatobiliary disorders			Hepatitis, including jaundice
Skin and subcutaneous tissue disorders		Skin rash	Photosensitivity, hair loss, sweating,
			urticaria, exfoliative dermatitis,
Musculoskeletal and connective tissue disorders		Myalgia	Extrapyramidal effects with muscle spasms, dystonia,
			muscle weakness
Renal and urinary disorders		Urinary retention, dysuria, urinary difficulty	Urinary frequency

General disorders and administrative site conditions		Fatigue	

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

Ascorbic acid

System organ class	Less frequent	Frequency unknown (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Haemolysis (in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency)
Nervous system disorders		Headache
Vascular disorders		Flushing
Gastrointestinal disorders	Diarrhoea, gastrointestinal disturbances	
		Nausea, vomiting, stomach cramps
Skin and subcutaneous tissue disorders		Redness of skin
Renal and urinary disorders		Formation of renal calcium oxalate calculi
General disorders and administrative site conditions		Tolerance

Chlorphenamine/Pseudoephedrine/Paracetamol combination

System organ class	Frequent
Nervous system disorders	Dizziness, somnolence
Gastrointestinal disorders	Dry mouth
General disorders and administrative site conditions	Asthenia

Post-marketing:

System organ class	Frequency unknown (cannot be estimated from the available data)
Immune system disorders	Anaphylactic reaction, hypersensitivity
Psychiatric disorders	Anxiety, euphoric mood, hallucination, visual hallucination, restlessness
Nervous system disorders	Cerebrovascular accident, headache, paraesthesia, psychomotor hyperactivity, tremor
Cardiac disorders	Dysrhythmia, myocardial infarction, palpitations, tachycardia
Gastrointestinal disorders	Abdominal pain, colitis ischaemic, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis, angioedema, fixed eruption, pruritus, rash, pruritic rash, urticaria
Renal and urinary disorders	Dysuria, urinary retention
	Patients known to be at risk of hyperoxaluria should not ingest ascorbic acid doses exceeding 1 g daily as there may be increased urinary oxalate excretion. However, such risk has not been demonstrated in normal, non-hyper oxaluric individuals. Increased intake of ascorbic acid over a prolonged period may result in increased renal clearance of ascorbic acid, and deficiency may result if the intake is reduced or withdrawn rapidly. Doses of more than 600mg daily have a diuretic effect. Ascorbic acid has been implicated in precipitating haemolytic anaemia in certain individuals deficient of glucose-6-phosphate dehydrogenase
Investigations	Increased blood pressure, increased transaminases

b) Description of selected adverse reactions

*Ascorbic acid should be given with care to patients with hyperoxaluria.

**Large doses of ascorbic acid may cause diarrhoea

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 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

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Paracetamol

Symptoms

Nausea, vomiting and anorexia. Liver damage, which may be fatal, may only appear after a few days. Acute intoxication may cause kidney failure.

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

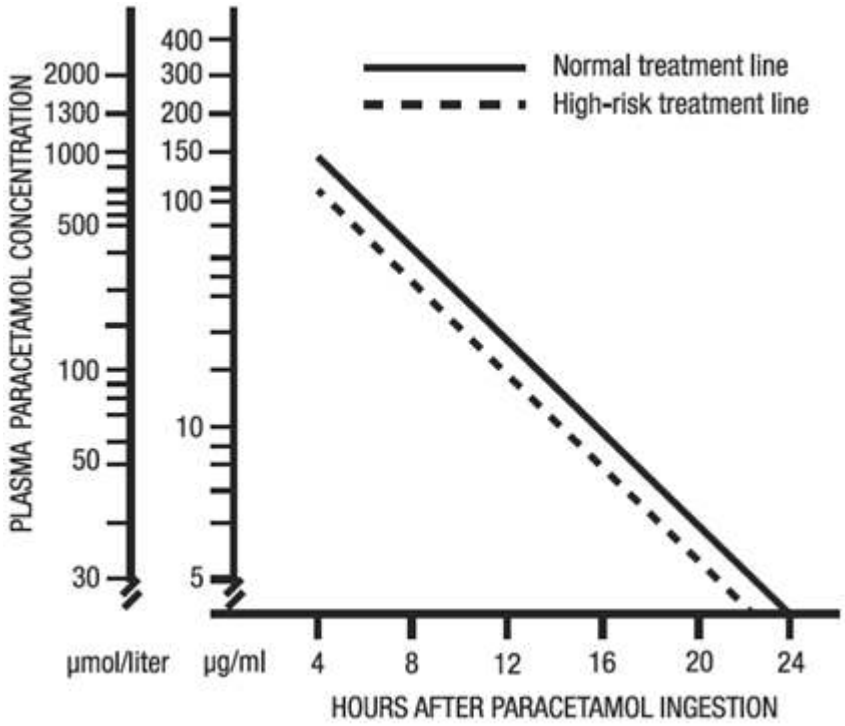
Treatment of paracetamol overdosage:

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 four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen 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 four hours for seventeen 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

Symptoms

Chlorphenamine overdosage may be fatal especially in infants and children.

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 and death may occur within 18 hours.

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

Treatment

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

Symptoms

Pseudoephedrine overdosage produces central nervous system stimulation with excitement, restlessness, rapid speech, hallucinations, hypertonicity and hyperflexia with dilated pupils.

Convulsions in children due to cerebral stimulation. In adults, symptoms of stimulation include insomnia, nervousness, tachycardia, tremors, muscle twitching and convulsions.

Severe cardiovascular repercussions include hypertension, angina, dysrhythmias, myocardial infarction and cerebral haemorrhage.

Treatment

Potassium supplements may be required. Tachycardia.Beta-blockers may be administered for tachycardia.

To enhance elimination:

Forced diuresis will increase elimination of pseudoephedrine provided renal function is adequate; however, diuresis is not recommended for severe overdosage.

Specific treatment:

For delirium or convulsions, intravenous diazepam may be administered.

The cardiac state should be monitored and serum electrolytes measured. If there are signs of cardiac toxicity, intravenous propranolol may be indicated.

Hypokalaemia may be treated, if necessary, with a slow infusion of a dilute potassium chloride solution; serum potassium concentration should be monitored during and for several hours after administration of potassium chloride.

Consult a doctor or take the patient to the nearest hospital immediately.

Specialised treatment is essential as soon as possible.

The latest information regarding the treatment of overdosage can be obtained from the nearest poison centre.

Ascorbic acid

Symptoms

At doses of over 3 g per day unabsorbed ascorbic acid is mainly excreted unmetabolised in the faeces. Absorbed ascorbic acid additional to the body's needs is rapidly eliminated. Large doses of ascorbic acid may cause diarrhoea and the formation of renal oxalate calculi. Symptomatic treatment may be required.
Ascorbic acid may cause acidosis or haemolytic anaemia in certain individuals with a deficiency of glucose 6-phosphate dyhydrogenase. Renal failure can occur with massive ascorbic acid overdosage.

Treatment

General supportive measures should be employed as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 5.8 Preparations for the common cold including nasal decongestants and antihistaminics.

Pharmacotherapeutic group: Other cold preparations

ATC code: R05X

Mechanism of action

FLUSIN S EFFERVESCENT has analgesic, anti-pyretic, decongestant 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.

Pseudoephedrine hydrochloride

Pseudoephedrine is a sympathomimetic vasoconstrictor with properties that can produce tachycardia, increased blood pressure, and CNS stimulation. Pseudoephedrine has alpha and beta adrenergic activity and some stimulant effect on the central nervous system. The sympathomimetic effect of pseudoephedrine produces vasoconstriction which in turn relieves nasal congestion.

Paracetamol

Paracetamol has analgesic and antipyretic effects.

Ascorbic acid

Ascorbic acid, coupled with dehydroascorbic acid to which it is reversibly oxidised, has a variety of functions in cellular oxidation processes. Ascorbic acid is required in several important hydroxylations, including the conversion of proline to hydroxyproline (and thus in collagen formation e.g. for intercellular substances and during wound healing); the formation of the neurotransmitters 5-hydroxytryptamine from tryptophan and noradrenaline from dopamine, and the biosynthesis of carnatine from lysine and methionine. Ascorbic acid

appears to have an important role in metal ion metabolism, including the gastrointestinal absorption of iron and its transport between plasma and storage organs. There is evidence that ascorbic acid is required for normal leucocyte functions and that it participates in the detoxification of numerous foreign substances by the hepatic microsomal system.
Deficiency of ascorbic acid leads to scurvy, which may be manifested by weakness, fatigue, dyspnoea, aching bones, perifollicular hyperkeratoses, petechia and ecchymosis, swelling and bleeding of the gums, hypochromic anaemia and other haematopoietic disorders, together with reduced residence to infections and impaired would healing.

5.2. Pharmacokinetic properties

Chlorphenamine maleate

Absorption

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract and its absorption is sensitive to various gastrointestinal local conditions such as foods, fluid volume and formulations. The small intestine is considered the primary site of absorption due to the available surface area and the basic nature of the parent chlorphenamine.
Complete absorption from the gastrointestinal tract was demonstrated by a low amount of medicine detected in faeces for 48 hours post-administration.
The oral bioavailability of chlorphenamine, however, is incomplete due to extensive gut and hepatic first pass metabolism, with the medicine reaching [~~and~~] peak plasma concentrations occur about 2,5 to 6 hours after oral doses and effects usually last 4 to 6 hours.

Distribution

Chlorphenamine appears to undergo considerable first-pass distribution to the lungs, kidneys, liver, milk and brain. About 70 ± 3 % of chlorphenamine in the circulation is bound to plasma proteins.

Biotransformation

Chlorphenamine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 41 ± 16 % having been reported. It is extensively metabolised in the liver by demethylation to mono- and didesmethylchlorpheniramine. It also undergoes oxidative deamination to polar metabolites, an alcohol and an acid. Metabolism of chlorphenamine has been shown to be mediated by the cytochrome P450 isozyme CYP2D6.

Elimination

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.
Variability in the half-life of chlorphenamine and its metabolites has been historically attributed to the tubular reabsorption of non-ionised medicine from alkaline urine. The protonation of chlorphenamine in acidic urine limits reabsorption of charged medicine, whereas the excretion of uncharged medicine in alkaline urine is dependent upon urine flow rate. Recent studies have shown that differences in CYP2D6 polymorphism in individuals who are poor and extensive metabolisers of the medicine are responsible for such variation.

Chlorphenamine metabolites are excreted primarily in urine. Total body clearance ranges from 4,4 – 7,9 mL/min/kg in adults. Long half-lives of up to 330 hours have been seen in patients with renal impairment. Urinary excretion is dependent on urine pH and flow with 20 – 26,5 % of unchanged medicine being excreted in acidic urine in 24 hours but only 0,3 – 0,4 % being excreted in alkaline urine. Less than 1 % of medicine is excreted in the faeces. Age, dialysis, urinary pH and flow influence the elimination kinetics.

Pseudoephedrine hydrochloride

Absorption

Pseudoephedrine is extensively absorbed from the gastrointestinal tract and has an oral bioavailability of 100 % and a half-life of about 4,3 to 8 hours. When pseudoephedrine is taken after a high-fat meal, the absorption rate is decreased, resulting in about an hour delay in attaining maximum concentrations.

Following oral administration of a single 30 mg tablet, a mean maximum plasma concentration of 104 ± 19 ng/mL is attained in 1,46 ± 0,55 hours. Following oral administration of a single 60 mg dose as tablets, mean maximum plasma concentrations of 180 ± 30 and 232 ± 30 ng/mL are attained at 1,94 ± 0,86 and 1,96 ± 0,62 hours, respectively.

Distribution

The apparent volume of distribution for pseudoephedrine ranges from 2,3 to 3,3 L/kg. Up to 0,7 % of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3-fold higher than those in plasma. This milk/plasma drug concentration profile suggests low protein binding, although no protein plasma binding data in humans are available. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2,2 to 6,7 % of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

Biotransformation

In adults, only a minor fraction of pseudoephedrine is metabolised in the liver. About 1 % to 6,2 % of a dose undergoes N-demethylation to the metabolite, norpseudoephedrine, which is excreted in the urine.

Elimination

Pseudoephedrine is mainly eliminated by renal excretion as unchanged medicine. Most of an oral dose (43 % to 96 %) is excreted unchanged in the urine within 24 hours. In adults, the elimination half-life (t½) for both immediate- and extended-release pseudoephedrine ranges from 5,5 to 7,0 hours. Oral clearance of pseudoephedrine is approximately 7,3 to 7,6 mL/min/kg. Urinary pH affects the elimination t½ and clearance of pseudoephedrine due to extensive reabsorption in the renal tubules at alkaline pH; renal reabsorption is negligible at acidic pH. In a study in which participants received sodium bicarbonate to adjust their urine to an alkaline range and ammonium chloride tablets to adjust their urine to an acidic range, an alkaline urinary pH of 8,0 prolonged the t½ (range, 9,2 to 16,0 hours) and an acidic urinary pH of 5,0 reduced the t½ of pseudoephedrine (range, 3,0 to 6,4 hours). In a study which monitored but did not adjust urinary pH, the t½ of pseudoephedrine in urine ranged from 1,9 hours at pH 5,66 to 21 hours at pH 7,80.

Paracetamol

Absorption

Paracetamol is well absorbed after oral administration from the gastrointestinal tract, primarily in the small intestine. Absorption occurs by passive transport. The rate of oral absorption depends mainly upon the rate of gastric emptying. The relative bioavailability ranges from 85 % to 99 %. Peak plasma concentrations occur within 30 to 60 minutes after

oral dosing and the half-life in plasma is about 2 hours after therapeutic doses. For individual adults, maximum plasma concentrations occur within 1 hour following ingestion and range from 14,8 to 17,6 µg/mL for a single 1 000 mg dose. Maximum plasma concentrations at steady state after 1 000 mg doses every 6 hours range from 17,6 to 18,2 µg/mL.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids, except fat. A relatively small proportion (10 % to 25 %) of paracetamol is bound to plasma protein.

Biotransformation

Paracetamol is primarily metabolised in the liver and involves three main pathways: conjugation with glucuronide; conjugation with sulphate; and oxidation via cytochrome P450 enzyme pathway. The oxidative pathway forms a reactive intermediate, which is detoxified by conjugation with glutathione to form inert cysteine and mercapturic acid metabolites. The principal cytochrome P450 isoenzyme involved *in vivo* appears to be CYP2E1, although CYP1A2 and CYP3A4 were considered minor pathways based on *in vitro* microsomal data. Subsequently, both CYP1A2 and
CYP3A4 were found to have negligible contribution *in vivo*.

Elimination

The elimination half-life of paracetamol is about 1 to 3,5 hours. It is approximately one hour longer in neonates and in cirrhotic patients.

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.

Renal clearance of unchanged paracetamol is about 3,5 % of the dose.

Ascorbic acid

A vitamin supplement.

Absorption

Ascorbic acid is well absorbed from the gastro-intestinal tract.

Distribution

Ascorbic acid is widely distributed to all tissues.

Biotransformation

Body stores of ascorbic acid normally are about 1,5 g. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. Ascorbic acid additional to the body's needs, generally amounts above 200 mg daily.

Elimination

Ascorbic acid is rapidly eliminated; unmetabolised ascorbic acid and its inactive metabolic products are chiefly excreted in the urine. The amount of ascorbic acid excreted unchanged in the urine is dose-dependent and may be accompanied by mild diuresis.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Aspartame, citric acid anhydrous, colloidal silicon dioxide, ginger flavour 77903-31, light liquid paraffin, polyethylene glycol 6000, sodium bicarbonate, sodium carbonate anhydrous

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Keep out of reach of children.

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

Keep tube tightly closed.

Keep in original packaging until required for use.

6.5. Nature and contents of container

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.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

30/5.8/0001

9. DATE OF FIRST AUTHORISATION

07 March 1996

10. DATE OF REVISION OF TEXT

23 January 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Namibia: NS1 04/5.8/0470

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