Proposed professional information for SINUTAB® SINUS PAIN EXTRA STRENGTH

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

SINUTAB® SINUS PAIN EXTRA STRENGTH tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Pseudoephedrine hydrochloride	30 mg
Codeine phosphate	10 mg
Chlorphenamine maleate	2 mg
Paracetamol	500 mg

Sugar free.

3. PHARMACEUTICAL FORM

Tablets.

A slightly mottled, pink, round, biconvex tablet with a bisecting score on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic relief of severe sinus pain, including maxillary, frontal or facial pain. Also for associated malaise, fever and congestion of the nasal sinus and Eustachian tube mucosa,

including the symptomatic relief of hay fever, influenza and the common cold.

4.2 Posology and method of administration

Adults and children over 12 years:

One to two tablets every four to six hours.

Do not exceed eight tablets in 24 hours.

Children aged less than 12 years:

Not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

DO NOT EXCEED THE RECOMMENDED DOSE.

4.3 Contraindications

- Hypersensitivity to chlorphenamine maleate, codeine phosphate, paracetamol, pseudoephedrine, or to any of the ingredients (see section 4.8).
- Contraindicated in persons receiving monoamine oxidase inhibitor treatment or within 14 days of ceasing such treatment.
- Chronic respiratory insufficiency.
- Kidney disease.
- Severe liver function impairment.
- Contraindicated in most forms of cardiovascular disease, including angina and hypertension, hyperthyroidism, hyperexcitability, phaeochromocytoma and closed angle glaucoma.
- Pseudoephedrine should be avoided in patients undergoing anaesthesia with halothane or other halogenated anaesthetic medicines.

4.4 Special warnings and precautions for use

Stop use and consult a doctor if pain or fever persists or gets worse at the recommended dosage, if new symptoms occur or if redness and swelling are present, as these could be signs of a more serious condition.

Do not use SINUTAB® SINUS PAIN EXTRA STRENGTH continuously without consulting a doctor:

- for pain: for more than 5 days in adults and children over 12 years of age.
- for fever: for more than 3 days.

Dosages in excess of those recommended may provoke severe liver, kidney and cardiovascular repercussions.

SINUTAB® SINUS PAIN EXTRA STRENGTH may lead to drowsiness and impaired concentration which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressant medicines.

Do not use SINUTAB® SINUS PAIN EXTRA STRENGTH with alcohol. Ask a doctor or pharmacist before use with benzodiazepines, sedatives, tranquilizers or other central nervous system depressants.

SINUTAB® SINUS PAIN EXTRA STRENGTH contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Do not use SINUTAB® SINUS PAIN EXTRA STRENGTH without consulting a doctor or pharmacist if you are presently taking monoamine oxidase inhibitors or other medicines for depression, psychiatric or emotional conditions, or hypertension or other cardiovascular conditions, particularly those with coronary heart disease (see section 4.5).

Do not take concurrently with any other paracetamol- or sympathomimetic-containing medicines

(see section 4.3).

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving paracetamol.
Patients should be informed about the signs of serious skin reactions and use of SINUTAB® SINUS PAIN EXTRA STRENGTH should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities (more than 8 tablets in 24 hours) of SINUTAB® SINUS PAIN EXTRA STRENGTH.
Codeine is not recommended in patients with severe hepatic impairment because codeine is not converted to morphine leading to poor analgesia.

Use with caution in renal disease. Patients with known renal disease should consult their healthcare provider for guidance relating to their dosage.

Exceeding the prescribed dose, together with prolonged and continuous use of SINUTAB® SINUS PAIN EXTRA STRENGTH, may lead to dependency and addiction.

Codeine is not recommended in adolescents 12 to under 18 years of age for pain.

Even at recommended dosages, ultra-rapid metabolisers of codeine may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness,

confusion, or shallow breathing).

Use of SINUTAB® SINUS PAIN EXTRA STRENGTH should be discontinued, and quick medical attention should be sought at the earliest sign of codeine toxicity including symptoms such as extreme sleepiness, confusion, or shallow breathing which may be life threatening.

Codeine should be used with caution in patients with convulsive disorders, head injuries, and in conditions in which intracranial pressure is raised.

Hyperalgesia may occur with the use of opioids, particularly at high doses. An unexplained increase in pain, or increased levels of pain can occur with increasing opioid dosages.
SINUTAB® SINUS PAIN EXTRA STRENGTH may cause urinary retention in patients with prostatic hyperplasia. Tolerance with dependence may occur after continued use.
The effects of pseudoephedrine hydrochloride are lessened by medicines containing guanethidine, reserpine, methyldopa and may be diminished or enhanced by tricyclic anti-depressants.
SINUTAB® SINUS PAIN EXTRA STRENGTH may increase blood pressure and therefore special care is advisable in patients receiving antihypertensive therapy.

SINUTAB® SINUS PAIN EXTRA STRENGTH should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.
Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) have been reported with pseudoephedrine-containing medicines, such as SINUTAB® SINUS PAIN EXTRA STRENGTH. 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.

SINUTAB® SINUS PAIN EXTRA STRENGTH should be given with caution to patients with persistent respiratory conditions such as emphysema, chronic bronchitis, bronchial asthma, or where cough is accompanied by excessive secretions, chronic pulmonary disease, hypothyroidism, diabetes, adrenocortical insufficiency, impaired kidney or liver function, obesity, obstructive sleep apnoea, prostatic hyperplasia and shock. It should be used with caution with patients with inflammatory or obstructive bowel disorders, or myasthenia gravis.
The dosage should be reduced in elderly and debilitated patients.

The prolonged use of high doses of codeine has produced dependence of the morphine type.
Avoid concurrent use of medicines containing the same or similar ingredients.
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver or kidney damage.

4.5 Interaction with other medicines and other forms of interaction

Alcohol and medicines that induce liver enzymes can increase the toxicity of SINUTAB® SINUS PAIN EXTRA STRENGTH.
Concurrent use of SINUTAB® SINUS PAIN EXTRA STRENGTH and hepatotoxic medicines may increase the risk of hepatotoxicity.
Concurrent use with enzyme-inducing medicines may also increase the risk of hepatotoxicity. The absorption of SINUTAB® SINUS PAIN EXTRA STRENGTH may be accelerated when used with metoclopramide.

Absorption of SINUTAB® SINUS PAIN EXTRA STRENGTH is reduced if given within one hour of cholestyramine.

Prolonged use of SINUTAB® SINUS PAIN EXTRA STRENGTH with salicylates increases the risk of adverse renal effects.

SINUTAB® SINUS PAIN EXTRA STRENGTH may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics, and other medicines with anticholinergic properties such as tricyclic antidepressants.

SINUTAB® SINUS PAIN EXTRA STRENGTH may reverse the action of certain cardiovascular medications and therefore special care is advisable in patients receiving such therapy.

Concomitant use with other sympathomimetic medicines, such as decongestants, tricyclic antidepressants and appetite suppressants or with monoamine oxidase inhibitors, which interfere with the catabolism of sympathomimetic amines, may cause a rise in blood pressure. An increased risk of arrhythmias may also occur if given to patients receiving cardiac glycosides, quinidine or tricyclic antidepressants. There is an increased risk of vasoconstrictor or pressor effect in patients receiving ergot alkaloids, oxytocin or other vasoconstrictors.

Interactions are possible with guanethidine, reserpine, tricyclic antidepressants, digoxin and alpha methyldopa.

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

Aluminium hydroxide-containing medicines may increase the absorption rate of SINUTAB® SINUS PAIN EXTRA STRENGTH.

The depressant effects of SINUTAB® SINUS PAIN EXTRA STRENGTH is enhanced by medicines which depress the action of the central nervous system, such as alcohol, anaesthetics, hypnotics and sedatives, phenothiazines and tricyclic antidepressants.

Patients should be instructed to ask a doctor or pharmacist before use if they are taking warfarin or other coumarin derivatives.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery, or performing hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Paracetamol:

Blood and lymphatic system disorders:

Less frequent: Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia, anaemia.

Gastrointestinal disorders:

Less frequent: Pancreatitis

Hepato-biliary disorders:

Less frequent: Hepatitis.

Skin and subcutaneous tissue disorders:

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

Renal and urinary disorders:

Less frequent: Renal colic, renal failure and sterile pyuria.

Chlorphenamine maleate:

Blood and lymphatic system disorders

Less frequent: agranulocytosis, leucopenia, haemolytic anaemia and thrombocytopenia

Immune system disorders

Less frequent: hypersensitivity reactions such as pruritus or rash

Psychiatric disorders

Less frequent: nervousness, euphoria, irritability, nightmares, hallucinations

Nervous system disorders

Frequent: sedation, varying from slight drowsiness to deep sleep, including lassitude, dizziness and incoordination

Less frequent: insomnia, tremors, convulsions, headache, blurred vision, paraesthesias extrapyramidal effects

Ear and labyrinth disorders

Less frequent: tinnitus

Vascular disorders

Less frequent: hypertension, hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: thickened respiratory-tract secretions and tightness of the chest

Gastrointestinal disorders

Less frequent: nausea, vomiting, dry mouth, constipation, gastric reflux, diarrhoea, epigastric pain

Musculoskeletal and connective tissue disorders

Less frequent: myalgia

Renal and urinary disorders

Less frequent: urinary difficulty and retention

General disorders and administration site conditions

Less frequent: Sweating, hair loss

Pseudoephedrine hydrochloride:

Metabolism and nutrition disorders

Less frequent: decreased appetite, hypokalaemia, altered metabolism

Psychiatric disorders

Frequent: fear, anxiety, insomnia, confusion, irritability, psychotic states

Nervous system disorders

Frequent: restlessness, tremor, dizziness

Less frequent: cerebral haemorrhage, headache

Cardiac disorders

Less frequent: pulmonary oedema, cardiac arrythmias, anginal pain, palpitations, and cardiac arrest

Vascular disorders

Less frequent: hypertension, reflex bradycardia, tachycardia, hypotension, fainting

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea

Gastrointestinal disorders

Less frequent: nausea, vomiting, hypersalivation

Renal and urinary disorders

Less frequent: difficulty in micturition, urinary retention.

General disorders and administration site conditions

Frequent: weakness, sweating, tolerance with dependence

Investigations

Less frequent: changes in blood sugar levels

Codeine phosphate:

The following side-effects have been reported but frequencies are unknown.

Psychiatric disorders

Restlessness, changes of mood, hallucinations.

Nervous system disorders

Drowsiness and confusion. Dry mouth, dizziness, sweating, facial flushing, headache, vertigo.

Raised intracranial pressure.

Eye disorders

Miosis.

Cardiac disorders

Bradycardia, tachycardia, palpitations.

Vascular disorders

Orthostatic hypotension.

Gastrointestinal disorders

The most common side effects are nausea, vomiting, constipation.

Skin and subcutaneous tissue disorders

Due to the histamine-releasing effect, reactions such as urticaria, pruritus and itching of the nose may occur.

Renal and urinary disorders

Micturition may be difficult and there may be ureteric or biliary spasm.

Reproductive system and breast disorders

Decreased libido or impotence.

General disorders and administration site conditions

Hypothermia.

Post-marketing experience:

The following adverse drug reactions were identified during post-marketing experience with chlorpheniramine, codeine, paracetamol, pseudoephedrine by frequency category estimated from clinical trials or epidemiology studies:

Immune system disorders:

Frequency unknown: Anaphylactic reaction, hypersensitivity.

Psychiatric disorders:

Frequency unknown: Anxiety, euphoric mood, hallucination, visual hallucination, restlessness.

Nervous system disorders:

Frequency unknown: Cerebrovascular accident, headache, paraesthesia, psychomotor hyperactivity, tremor.

Cardiac disorders:

Frequency unknown: Dysrhythmia, myocardial infarction, palpitations, tachycardia.

Respiratory, thoracic and mediastinal Disorders

Frequency unknown: Respiratory depression.

Gastrointestinal disorders:

Frequency unknown: Abdominal pain, ischaemic colitis, diarrhoea, vomiting.

Skin and subcutaneous tissue disorders:

Frequency unknown: Acute generalised exanthematous pustulosis, angioedema, dermatitis, fixed eruption, pruritus, rash, pruritic rash, urticaria.

Renal and urinary disorders:

Frequency unknown: Dysuria, urinary retention.

Investigations:

Frequency unknown: Increased blood pressure, increased transaminases.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of SINUTAB® SINUS PAIN EXTRA STRENGTH is important. It allows continued monitoring of the benefit/risk balance of SINUTAB® SINUS PAIN EXTRA STRENGTH. 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

For further information, please contact the Johnson and Johnson call centre on 0860 410032 (landline).

4.9 Overdose

Paracetamol:

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 antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses

(greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later, after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 – 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four 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 stuporous 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 eight 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.

An initial dose of 150 mg/kg *N*-acetylcysteine in 200 ml dextrose injection given **intravenously**

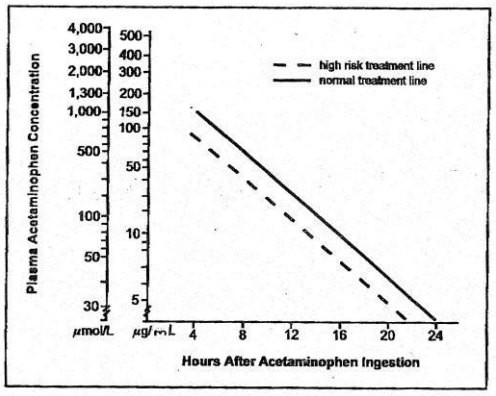
over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours.

The volume of intravenous fluid should be modified for children.

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with *N*-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time after ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

Plasma Paracetamol Concentration



Adapted from Smilkstein et al. Ann Emerg Med 1991;20:1059

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:

Overdosage with chlorphenamine may be fatal, especially in infants and children, in whom the main symptoms are central nervous system stimulation and antimuscarinic effects, including ataxia, excitement, hallucinations, muscle tremor, convulsions, dilated pupils, dry mouth, flushed face and hyperpyrexia. Deepening coma, cardiorespiratory collapse, and death may occur within 18 hours. In adults the usual symptoms are central nervous system depression with drowsiness, coma and convulsions. Hypotension may also occur.

Pseudoephedrine hydrochloride:

Convulsions and hyperpyrexia 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, arrhythmias, myocardial infarction and cerebral haemorrhage.

Treatment of overdose:

To decrease absorption:

Because pseudoephedrine is rapidly absorbed from the gut, emetics should be instituted within 4 hours of overdosage in order to be effective. Charcoal is useful only if administered within 1 hour.

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.

Codeine phosphate:

Produces central stimulation with excitation and in children, convulsions, followed by vomiting, drowsiness, respiratory depression and cyanosis and coma.

Treatment: Symptomatic and supportive. Future gastrointestinal absorption can be limited by repeated doses of activated charcoal.

Naloxone hydrochloride is used to counteract the respiratory depression and coma produced by excessive doses of codeine. A dose of 0,4 to 2 mg is given intravenously, repeated at intervals of 2 to 3 minutes. In children a dose of 0,01 to 0,1 mg per kg body weight may be given similarly. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Other analgesics and antipyretics: paracetamol, combinations excl. psycholeptics

ATC code: N02BE51

Paracetamol has analgesic and antipyretic properties. It acts predominantly by inhibiting prostaglandin synthesis in the central nervous system.

Pseudoephedrine hydrochloride acts as a decongestant. It is a direct- and indirect-acting sympathomimetic.

Chlorphenamine maleate, an alkylamine derivative, has antihistaminic properties. Codeine phosphate is an opioid analgesic.

5.2 Pharmacokinetic properties

Absorption:

Chlorphenamine

Chlorphenamine is slowly absorbed 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 peak plasma concentrations of ~ 32 ng/mL in adults with a 4 mg oral dose at approximately 6 hours.

Codeine

Codeine is rapidly and well absorbed following tablet and liquid oral administration with a bioavailability of 50 – 80 %. Codeine can be detected in plasma as early as 0,17 to 1 hour (h) after oral administration. T_{max} of codeine 30 mg and 60 mg occurred at 0,75 to 1 h and 0,61 to 1,3 h with C_{max} of 61 to 89,1 ng/mL and 122,8 to 214,2 ng/mL, respectively. AUC for codeine 30 mg and 60 mg are 216 to 354,6 ng·h/mL and 417 to 734 ng·h/mL.

Codeine can be taken with or without food.

Paracetamol

Oral paracetamol is rapidly and almost completely absorbed 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 are usually attained about 30 – 60 minutes after oral dosing. 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.

Pseudoephedrine

Pseudoephedrine is rapidly absorbed from the gastrointestinal tract. The oral bioavailability of pseudoephedrine is high, as determined by urine collections greater than 96 % of administered doses. 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.

Distribution:

Chlorphenamine

Chlorphenamine undergoes a rapid and extensive distribution to the lungs, kidneys, liver, milk and brain. The apparent volume of distribution is approximately 7 L/kg for adults after oral dosing. Chlorphenamine is highly protein bound (~ 70 %).

Codeine

Codeine enters the tissues rapidly and is concentrated in the kidney, lung, liver and spleen. Codeine is less than 10 % protein bound with an apparent volume of distribution between 3 to 4 L/kg.

Paracetamol

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is 0,7 to 1 L/kg in children and adults. A relatively small proportion (10 % to 25 %) of paracetamol is bound to plasma protein.

Pseudoephedrine

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.

Metabolism:

Chlorphenamine

Chlorphenamine undergoes extensive gut and hepatic first pass metabolism with an absolute bioavailability of 25 to 50 %. 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.

Codeine

Codeine is metabolized by O- and N-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Approximately 50 % undergoes pre-systemic metabolism in the gut and liver.

Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. A significant proportion of the population are poor or rapid metabolisers of codeine due to genetic differences in metabolism. As a result, they experience unpredictable opioid analgesic effects or adverse effects. Ethnicity is a factor in the occurrence of CYP2D6 variability. Patients, who are poor CYP2D6 metabolisers (PMs), have a deficiency or are completely lacking this enzyme and will not obtain the adequate effect.

Paracetamol

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*.

Pseudoephedrine

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:

Chlorphenamine

Mean half lives in adults administered as a 4 mg oral tablet range from 20 to 30 hours. 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.

Codeine

Codeine and its active metabolites such as morphine are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Only 3 % to 16 % of a given dose of codeine, when taken as a single ingredient or with paracetamol, is excreted unchanged in urine. The $t_{½}$ for codeine 30 mg and 60 mg is 1,5 to 2,2 h and 2,1 to 4,5 h, respectively. For codeine taken with paracetamol, $t_{½}$ is similar to single ingredient codeine. However, in a study of patients on haemodialysis, the mean $t_{½}$ was 13 ± 3,3 h compared to healthy subjects in the study with $t_{½}$ of 4,5 ± 0,8 h. Renally impaired patients should be dosed and titrated carefully due to possible drug and metabolite accumulation.

Codeine has a reported systemic clearance of 252 mL/min and the clearance for codeine when taken with paracetamol is 291 mL/min. Although no specific dosing recommendations are available for patients with hepatic dysfunction, smaller doses and prolonged dosing intervals should be considered to avoid drug accumulation.

Paracetamol

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. Paracetamol is eliminated from the body as glucuronide (45 – 60 %) and sulphate (25 – 35 %) conjugates, thiols (5 – 10 %) as cysteine and mercapturate metabolites, and catechols (3 – 6 %) that are excreted in the urine. Renal clearance of unchanged paracetamol is about 3,5 % of the dose.

Pseudoephedrine

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium phosphate dihydrate dibasic

Colloidal silicon dioxide

Crospovidone

FD & C Red no. 3

Magnesium stearate

Povidone

Pregelatinised maize starch

Pregelatinised starch

Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

Protect from light and moisture.

Do not remove tablets from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

PVC/aluminium blister packs containing 12 and 24 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

SOUTH AFRICA

8. REGISTRATION NUMBER

37/5.8/0139

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 August 2009

10. DATE OF REVISION OF THE TEXT

9 December 2021