PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME (and dosage form):

ASTRAPAIN FORTE TABLETS

COMPOSITION:

Each tablet contains:	Paracetamol	320 mg
	Codeine Phosphate	8 mg
	Caffeine anhydrous	32 mg
	Meprobamate	150 mg
	Preservative: Nipastat	0,025% (m/m)

Contains TARTRAZINE.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 2.8 Analgesic combinations

PHARMACOLOGICAL ACTION:

Paracetamol has analgesic and antipyretic properties.

Codeine is metabolized to morphine, which in turn, exerts an analgesic effect.

Caffeine relaxes smooth muscle and stimulates the central nervous system (CNS).

Meprobamate acts in the central nervous system, has sedative and hypnotic properties.

PHARMACOKINETICS:

Paracetamol: Absorption following oral administration is rapid and almost complete. Paracetamol is metabolized in the liver primarily by conjugation. Paracetamol has half-life of 1 to 4 hours, time to peak concentration of 0.5 to 2 hours, time to peak effect of 1 to 3 hours and the duration of action of 3 to 4 hours. Paracetamol is renally excreted primarily as metabolites and 3% of a dose may be excreted unchanged.

Codeine: Readily absorbed from the gastrointestinal tract. Half-life is 2.5 to 4 hours. Codeine is metabolized in the liver. The cytochrome P450 enzyme 2D6 converts codeine to morphine, one of its metabolites. About 10% of the dose is demethylated to morphine. Onset of action is 30 to 45 minutes. The time to peak effect is 1 to 2 hours. Duration of action is 4 hours. Codeine is eliminated via the kidneys.

Caffeine: Caffeine is readily absorbed after oral administration. Readily distributed to all body compartments, readily crosses the placenta and blood brain barrier.

Protein binding is about 25 % - 36 %. It is biotransformed in the liver. Its half life is 3 to 7 hours. Peak plasma concentration is reached within 50 to 75 minutes following oral administration. Elimination is renally

Meprobamate: Meprobamate is well absorbed from the gastrointestinal tract. Its plasma half life is about 10 hours. Its metabolism takes place in the hepatic system. It is excreted renally, about 8% - 19% of it is excreted unchanged.

INDICATIONS:

Pain and pain associated with tension.

Short term use in mild to moderate pain associated with anxiety or tension.

CONTRA-INDICATIONS:

Hypersensitivity to any of the ingredients.

It should not be administered to patients with acute intermittent porphyria.

Patients with renal or hepatic insufficiency.

Use of **ASTRAPAIN FORTE TABLETS** during pregnancy should be avoided.

Asthma, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, head injuries and conditions in which intracranial pressure is raised, heart failure secondary to chronic lung disease, a history of cardiac disease, epilepsy, and all convulsive states, patients taking monoamine oxidise inhibitors or within 14 days of stopping such treatment.

Porphyria.

WARNINGS:

The use of this medicine leads to drowsiness which is aggravated by the simultaneous intake of alcohol and it is dangerous to drive a vehicle or be in charge of machinery while on treatment with this product.

Paracetamol administration in excess of the recommended dosage may cause severe liver damage.

In the event of overdosage or suspected overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison control centre must be contacted immediately.

This product contains FD & C Yellow No 5 (Tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of Tartrazine sensitivity in the general population is currently thought to be low, it is frequently seen in patients who also have aspirin sensitivity.

Codeine: Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction.

INTERACTIONS:

Due to codeine, **ASTRAPAIN FORTE TABLETS** may affect the activity of other medicines by delaying the absorption. The depressant effects are aggravated by alcohol, anaesthetics, hypnotics sedatives, tricyclic antidepressants and phenothiazines.

Hepatotoxic medicines – Increased risk of hepatoxicity.

Enzyme inducing medicines – Increased risk of hepatoxicity.

Possible decrease in therapeutic effects of **ASTRAPAIN FORTE TABLETS.**

Metoclopramide – Absorption of **ASTRAPAIN FORTE TABLETS** may be accelerated.

Cholestyramine – Absorption of **ASTRAPAIN FORTE TABLETS** is reduced if given within one hour of cholestyramine.

Prolonged concurrent use of **ASTRAPAIN FORTE TABLETS** with salicylates increases the risk of adverse renal effects.

- Due to the active caffeine, which undergoes extensive metabolism by hepatic microsomal cytochrome P450, **ASTRAPAIN FORTE TABLETS** is subject to numerous interactions with other medicines which enhance or reduce its metabolic clearance.
- **ASTRAPAIN FORTE TABLETS** may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, opioid analgesics.
- **ASTRAPAIN FORTE TABLETS** has an additive antimuscarinic action with other antimuscarinic medicines such as atropine and antidepressants (both tricyclic and monoamineoxidase inhibitors.)

ASTRAPAIN FORTE TABLETS may enhance the metabolism of oral contraceptives, corticosteroids, phenytoin, phenothiazines and tricyclic antidepressants.

PREGNANCY AND LACTATION.

Safety and efficacy in pregnancy and lactation have not been established.

DOSAGE AND DIRECTIONS FOR USE:

DO NOT EXCEED THE RECOMMENDED DOSE.

Not recommended for children under the age of 12 years.

Adults: Two tablets every 6 to 8 hours.

Not to be used for longer than 10 days. *

SIDE - EFFECTS AND SPECIAL PRECAUTIONS:

SIDE EFFECTS: *

Paracetamol:

Blood and the lymphatic system disorders:

Less frequent: Neutropenia, pancytopenia and leucopenia.

Skin and subcutaneous tissue disorders:

Less frequent: Skin reactions and other allergic reactions may occur. This rash is usually erythematous or urticarial, but sometimes more serious and may be accompanied by fever and mucosal lesions.

Meprobamate:

Blood and lymphatic system disorders:

Less frequent: Agranulocytosis, eosinophilia, leucopenia, thrombocytopenia and aplastic anaemia.

Cardiac disorders:

Less frequent: Hypotension, tachycardia, and cardiac arrhythmias.

Eye disorders:

Less frequent: Disturbances of vision.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting, diarrhoea.

Nervous system disorders:

Less frequent: Drowsiness, paraesthesia, weakness, headache, paradoxical excitement, dizziness, ataxia.

Skin and subcutaneous tissue disorders:

Less frequent: Hypersensitivity reactions such as skin rashes, urticaria, purpura, angioedema, erythema multiforme and exfoliative or bullous dermatitis may occur. Symptoms of porphyria may be exacerbated.

Other disorders:

Less frequent: Bronchospasm or anuria.

Codeine:

Cardiac disorders:

Less frequent: Bradycardia, palpitation, hypotension, orthostatic hypotension, circulatory failure.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting, constipation.

Nervous system disorders:

Less frequent: Vertigo, hyperthermia, restlessness, deepening coma, euphoria, changes of mood, muscle rigidity, drowsiness, confusion, dry mouth, sweating, facial flushing.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, urticaria.

Urinary disorders:

Less frequent: Micturition may be difficult and there may be ureteric or biliary spasms and an diuretic effect.

Other disorders:

Less frequent: Respiratory depression, raised intracranial pressure and miosis.

Caffeine:

Gastrointestinal disorders:

Frequent: Nausea.

Nervous system disorders:

Frequent: Headache, insomnia, restlessness, excitement, muscle tremor.

SPECIAL PRECAUTIONS:

Codeine should be used with caution or in reduced doses in patients with adrenocortical insufficiency. Should be used with caution in patients with obstructive bowel disorders. Dosage should be reduced in debilitated and in elderly patients. Should be used with caution or reduced doses in patients with hypothyroidism. Should be used with caution in patients with liver impairment, myasthenia gravis, prostatic hypertrophy, impaired renal function or shock. Prolonged use of high doses of codeine may lead to dependence.

Caffeine should be taken with care by patients with a history of peptic ulceration or hyperacidity. With prolonged use some degree of tolerance and psychic dependence may occur.

Due to the dependence potential meprobamate should be gradually withdrawn after long term treatment. Meprobamate may lower the tolerance to alcohol and other central nervous system depressants.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Codeine phosphate:

Symptoms of overdosage with codeine phosphate include the following: nausea, vomiting, restlessness, sensory disturbances, muscle tremor, diuresis, palpitations, stupor, shock, central stimulation with exhilaration, convulsions, drowsiness, respiratory depression, hypotension with circulatory failure, respiratory collapse, cyanosis and coma.

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 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 drugs 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 stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

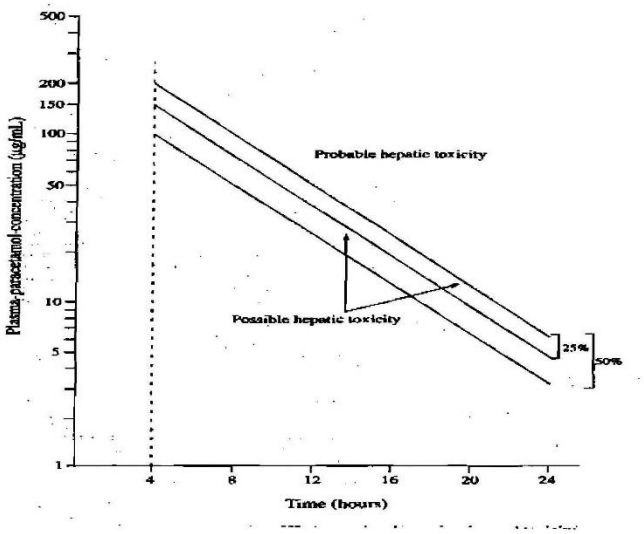
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg 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 1000 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, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the normogram below.

72 Analgesics Anti-inflammatory Drugs and Antipyretics

Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.



Monitor all patients with significant ingestions for at least ninety six hours.

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.

Meprobamate:

Symptoms are mainly due to the depressant effect on the central nervous system. See also “Side-Effects and Special Precautions”.

Following recent ingestion of an overdose the stomach may be emptied by gastric lavage and aspiration. Patients should be managed with intensive symptomatic and supportive therapy, with particular attention being paid to maintenance of cardiovascular, respiratory and renal functions, and to the maintenance of electrolyte balance.

IDENTIFICATION:

Green, round, biconvex tablet, bisected on the side, and embossed "GO PAIN" on the other side.

PRESENTATION:

Packaged in Aluminium foil/PVC push-through blister packs of 10 tablets per strip (packed in 20's or 100's per unit carton), or in round amber PVC jars containing 500 or 1 000 tablets.

STORAGE INSTRUCTIONS:

Store in a dry place below 25°C. Protect from strong light.

KEEP OUT OF REACH OF CHILDREN.

Blisters should not be removed from the carton until required for use.

REGISTRATION NUMBER:

27/2.8/0137

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

Astral Pharma (Pty) Ltd

125 Meade Street

George

6529

South Africa

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03 June 2011