Applicant: Astral Pharma (Pty) Ltd
Product name: ASTRAPAIN FORTE TABLETS
Dosage form and strength: Tablets, Paracetamol 320 mg, Codeine Phosphate 8 mg, Caffeine anhydrous 32 mg, Meprobamate 150 mg.

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ASTRAPAIN FORTE TABLETS, tablets.

2 QUALITIVE AND QUANTITIVE 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

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Green, round, flat tablet, bisected on the side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pain and fever, and pain associated with tension.

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

4.2 Posology and method of administration

Posology

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. *

Special populations

- Elderly population; dosage should be reduced in debilitated and in elderly patients (see section 4.4).

- Renal impairment; contraindicated in patients with renal insufficiency (see section 4.3).

- Hepatic impairment; contraindicated in patients with hepatic insufficiency (see section 4.3).

Paediatric population

Not recommended for children under the age of 12 years,

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of ASTRAPAIN FORTE TABLETS (see section 6.1).
- 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.
- After operations on the biliary tract.
- Acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raise.
- Heart failure secondary to chronic lung disease.
- Should not be given during an attack of bronchial asthma, a history of cardiac disease, epilepsy, and all convulsive states.
- Patients taking monoamine oxidise inhibitors or within 14 days of stopping such treatment.
- Porphyria.
- Children under the age of 12 years.
- Women who are breastfeeding their infants and women in the third trimester of pregnancy. (See section 4.6)

- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible for respiratory problems.

4.4 Special warnings and precautions for use

ASTRAPAIN FORTE TABLETS are not recommended for use by pregnant or breastfeeding women (see section 4.6).

Do not use continuously for more than ten days without consulting your doctor.

Consult your doctor if no relief is obtained with the recommended dosage.

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

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized 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 AstraPain Forte Tablets must immediately be discontinued and appropriate treatment instituted (see section 4.8).

Flucloxacillin

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 dose of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

This product 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 control centre must be contacted immediately.

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

Codeine:

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

Codeine should be used with caution or in reduced doses in patients with adrenocortical insufficiency. Should be used with caution in patients with inflammatory or 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, myasthenia gravis, prostatic hypertrophy, shock. Prolonged use of high doses of codeine may lead to dependence.

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, and phenothiazines.

The prolonged use of high doses of codeine has produced dependence of the morphine type.

Children with conditions associated with respiratory problems should not use codeine.

Codeine, as in **ASTRAPAIN FORTE TABLETS,** should be used in caution with patients with personal or family history of substance abuse or mental health because the risk of addiction is increased.

Patients with a history of cholecystectomy should consult a doctor before using **ASTRAPAIN FORTE TABLETS**, as it may cause acute pancreatitis in some patients.

Opioid-induced Hyperalgesia (OIH) and Allodynia

Opioid pain medicines have been associated with opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Increases in pain typically occur following a dose increase and resolve quicky following proper diagnosis and management of the condition. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinary non-painful stimuli (allodynia).

Caffeine

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.

Meprobamate

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 with consequent impairment of judgement and co-ordination. Symptoms of porphyria may be exacerbated (see section 4.3). Prolonged use of meprobamate may lead to the development of dependence of the barbiturate-alcohol type. Meprobamate may induce the hepatic microsomal enzymes involved in drug metabolism.

Tartrazine Warning

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.

4.5 Interaction with other medicines and other forms of interaction

- 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.

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Paracetamol, as in ASTRAPAIN FORTE TABLETS

Hepatotoxic medicines – Increased risk of hepatoxicity.

Enzyme inducing medicines – Increased risk of hepatoxicity.

Possible decrease in therapeutic effects of paracetamol.

Metoclopramide – Absorption of paracetamol may be accelerated.

Domperidone – Absorption of paracetamol may be accelerated.

Probenecid – Pre-treatment with probenecid can decrease paracetamol clearance and increase its half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Cholestyramine – Absorption of paracetamol is reduced if given within one hour of cholestyramine.

Salicylates - Prolonged concurrent use of paracetamol with salicylates increases the risk of adverse renal effects.

Antibiotics – Chronic use of isoniazid, an antibiotic medicine often prescribed for tuberculosis, may increase the risk of liver damage when combined with paracetamol, even at recommended doses.

Warfarin and anticoagulants – Concurrent, chronic, high-dose administration of paracetamol may increase the anticoagulant effect.

Paracetamol is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon) and isolated reports have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.

Antibacterials – The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing drugs such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone with other medicines for tuberculosis.

Antivirals – Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole. However, neither short-term nor long-term studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.

Interferon-alpha – Paracetamol has also been found to enhance the antiviral effect of interferon alfa.

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

Other medicines – paracetamol is metabolised in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or may induce this route (e.g. barbiturates, such as phenobarbitone, tricyclic antidepressants, alcohol, carbamazepine,

phenytoin, primidone, rifampicin, St John's wart (*Hypericum perforatum)* or other drugs that induce liver enzymes), causing hepatotoxicity, particularly in overdose.

Caffeine, as in ASTRAPAIN FORTE TABLETS

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers.

Caffeine may enhance the tachycardia effect of some decongestants.

Codeine, as in ASTRAPAIN FORTE TABLETS

ASTRAPAIN FORTE TABLETS may affect the activity of other medicines by delaying the absorption.

Metoclopramide and domperidone – Codeine may antagonize the effect of metoclopramide and domperidone on gastrointestinal motility.

Central nervous system medicines – The depressant effects are aggravated by alcohol, anaesthetics, hypnotics sedatives, tricyclic antidepressants and phenothiazines.

MAOI's – Opioid analgesics should be given with care to patients receiving monoamine oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

MAOI's taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOI) and result in serotonin syndrome. It is recommended that the product should not be taken concurrently or within two weeks of stopping treatment with a MAOI.

Sedative medicines such as benzodiazepines or related drugs - The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increase the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

4.6 Fertility, pregnancy and lactation

Pregnancy

ASTRAPAIN FORTE TABLETS should not be used during pregnancy (see section 4.3). This includes maternal use during labour because of the potential for respiratory depression in neonate.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

The patient should be advised of the risk of neonatal opioid withdrawal syndrome, and it should be ensured that appropriate treatment will be available.

Breastfeeding

Codeine, as in **ASTRAPAIN FORTE TABLETS,** should not be used during breastfeeding (see section 4.3), as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

At normal therapeutic doses, codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYPD2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
		Paracetamol	
Blood and the lymphatic system disorders:		Neutopenia (too few white blood cells) Pancytopenia (too few blood cells of all types) Leucopenia (too few white blood cells)	
Skin and subcutaneous tissue disorders:		Skin rashes and other allergic reactions may occur. This rash is usually erythematous (red skin rash) or urticarial (nettle rash), but sometimes more serious and may be accompanied by fever and mucosal lesions (deterioration of tissue due to injury or disease). Dermatitis, skin rashes, severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) / drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruption (FDE).	
		Meprobamate	
Blood and lymphatic system disorders		Agranulocytosis Eosinophilia, Leucopenia, Thrombocytopenia Aplastic anaemia	

Cardiac disorders		Hypotension Tachycardia Cardiac arrythmias	
Eye disorders		Disturbance of vision	
Gastrointestinal disorders		Nausea Vomiting Diarrhoea	
Nervous system disorders		Drowsiness Paraesthesia Weakness Headache Paradoxical excitement Dizziness Ataxia	
Skin and subcutaneous tissue disorders		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		Bronchospasm or anuria	
Codeine			
Cardiac disorders		Bradycardia Palpitation Hypotension Orthostatic hypotension Circulatory failure	
Gastrointestinal disorders		Nausea Vomiting Constipation	
Nervous system disorder		Vertigo Hyperthermia Restlessness Deepening coma Euphoria Changes of mood Muscle rigidity Drowsiness Confusion Dry mouth Sweating Facial flushing Orthostatic hypotension	

Skin and subcutaneous tissue disorders		Pruritis Urticaria	
Urinary disorders		Micturition may be difficult and there may be ureteric or biliary spasms and a diuretic effect.	
Other disorders		Respiratory depression Raised intracranial pressure and miosis	
Caffeine			
Gastrointestinal disorders	Nausea	Caffeine increases gastric secretions and may cause gastric ulceration.	
Nervous system disorders	Headache Insomnia Restlessness Excitement Muscle tremor		
Eye disorders		Scintillating scotoma	
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders		Tachycardia Extrasystoles	

Post marketing Experience:

Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicine. If a patient develops SCAR (Severe cutaneous adverse reactions), treatment with ASTRAPAIN FORTE TABLETS must immediately be discontinued and appropriate treatment instituted (see section 4.4).

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

4.9 Overdose

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.

Management:

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

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.

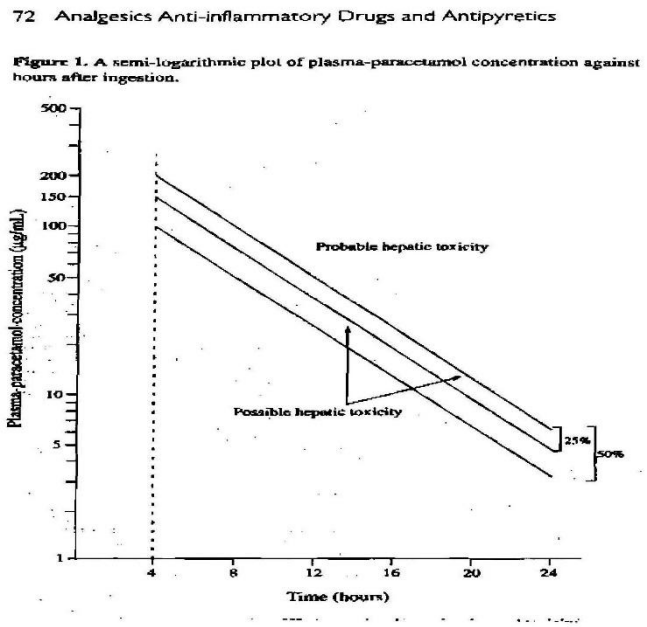
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage:

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 (IV)** 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. The nomogram should be used only in relation to a single acute 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.

For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity.

Meprobamate:

Symptoms are mainly due to the depressant effect on the central nervous system. See also “Undesirable effects and Special warnings and precautions for use”

Acute meprobamate overdosage can produce stupor, coma, convulsions, shock, circulatory and respiratory collapse.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic properties

Paracetamol

Absorption:

Absorption following oral administration is rapid and almost complete.

Biotransformation:

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.

Elimination:

Paracetamol is renally excreted primarily as metabolites and 3% of a dose may be excreted

unchanged.

Codeine

Absorption:

Readily absorbed from the gastrointestinal tract. Half-life is 2.5 to 4 hours.

Biotransformation:

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.

Elimination:

Codeine is eliminated via the kidneys.

Caffeine

Absorption:

Caffeine is readily absorbed after oral administration.

Distribution:

Readily distributed to all body compartments, readily crosses the placenta and blood brain barrier.

Biotransformation:

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:

Elimination is renally.

Meprobamate

Absorption:

Meprobamate is well absorbed from the gastrointestinal tract. Its plasma half life is about 10 hours.

Biotransformation:

Its metabolism takes place in the hepatic system.

Elimination:

It is excreted renally, about 8% - 19% of it is excreted unchanged.

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients are:

- Deep Apple Green (CI 19140/44090)

- Colloidal silicone dioxide (Aerosil 200)
- Magnesium stearate
- Nipastat
- Povidone 90 F
- Powdered Acacia
- Purified talc
- Starch, Maize

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place below 25°C.

Protect from strong light.

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

Store in the original package/container.

6.5 Nature and contents of container

Blister pack

- 10 tablets per blister (Aluminium foil/PVC push-through) packed in outer carton as 30 tablets.
- 20 tablets per blister (Aluminium foil/PVC push-through) packed in outer carton as 20, 40 or 100 tablets.

PVC jars

- 500 tablets in a round white PVC jar.
- 1000 tablets in a round white PVC jar.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 The holder of the certificate of registration

Astral Pharma (Pty) Ltd

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1683

South Africa

8 Registration number(S)

27/2.8/0137

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 November 1992

10 DATE OF REVISION OF TEXT

06 November 2025