Professional Information

SCHEDULING STATUS S2

1. NAME OF THE MEDICINE

PAINAMOL® PLUS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Paracetamol	500 mg
Codeine Phosphate	8 mg

Preservative:

Sodium metabisulphite 0,081 % *m/m*

Contains TARTRAZINE

Contains sugar: sucrose 20,0 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Flat yellow and red mottled tablet, scored on the one side and a "b" embossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PAINAMOL® PLUS tablets are indicated for the relief of mild to moderate pain and for the reduction of temperature in febrile conditions.

4.2 Posology and method of administration

Posology

Adults: One or two tablets every four to six hours.

Children over 12 years: One tablet every four to six hours.

Children 6 to 12 years: Half to one tablet every six hours.

Do not exceed an adult dose of 8 tablets per day.

Do not use continuously for longer than ten (10) days without consulting your doctor.

Method of Administration

For oral use.

4.3 Contraindications

- Hypersensitivity to **PAINAMOL® PLUS** or to any of the excipients listed in section 6.1.
- Codeine is contra-indicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and after operations on the biliary tract.
- In the presence of acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raised, during an attack of bronchial asthma.
- In heart failure secondary to lung disease.

4.4 Special warnings and precautions for use

Do not use continuously for more than 10 days without consulting your doctor.

Dosages in excess of those recommended may cause severe liver damage

Codeine should be given with extreme caution in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

Painamol® Plus tablets contain 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.

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

Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, myasthenia gravis, impaired renal function, impaired liver function, prostatic hypertrophy or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders. The dosage should be reduced in elderly and debilitated patients.

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

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

The administration of codeine during labour may cause respiratory depression in the new born infant.

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 **PAINAMOL PLUS** must immediately be discontinued and appropriate treatment instituted.

PAINAMOL® PLUS contains sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine

4.5 Interaction with other medicines and other forms of interaction

The speed of absorption of Paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of Paracetamol with increased risk of bleeding; occasional doses have no significant effect.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, primidone or rifampicin.

Excretion of paracetamol may be reduced and plasma concentrations increased when given with probenecid.

Hepatotoxicity at therapeutic doses of paracetamol has been reported in patients receiving isoniazid.

The depressant effects of Codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines. The hypotensive actions of diuretics and antihypertensive agents may be potentiated when used concurrently with opioid analgesics. Concurrent use of hydroxyzine with Codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

Concurrent use of Codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

The respiratory depressant effects caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

CNS depression or excitation may occur if Codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them. Quinidine can inhibit the analgesic effect of Codeine.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also

blocks the therapeutic effect of opioids.

Interference with laboratory tests: Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying, and with hepatobiliary imaging using technetium Tc99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increases biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dose. A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency. Codeine crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible association with respiratory and cardiac malformations has been reported.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. Use during pregnancy should be avoided if possible.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Codeine is contraindicated in women during breastfeeding (see section 4.3).

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, 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.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

Codeine may cause drowsiness, if affected patients should be advised not to drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Adverse Reaction**
Blood and the lymphatic system disorders	Frequency Unknown	agranulocytosis, thrombocytopenia, circulatory failure

Immune system disorders	Frequency Unknown	Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnoea, and anaphylactic reactions (including shock).
Psychiatric disorders	Frequency Unknown	Drug dependence (see section 4.4), Change in mood,restlessness
Nervous system disorders	Frequency Unknown	dizziness, light-headedness, confusion, drowsiness, raised intracranial pressure,deepening coma
Eye disorders	Frequency Unknown	Miosis
Ear and Labyrinth	Frequency Unknown	vertigo
Cardiac Disorders	Frequency Unknown	Bradycardia, palpitations
Vascular disorders	Frequency Unknown	Hypotension,facial flushing,orthostatic hypotension
Gastrointestinal disorders	Less Frequent	Acute pancreatitis, increased risk of abdominal pain
	Frequency Unknown	constipation, nausea, vomiting, dry mouth
Hepato-Biliary disorders	Frequency Unknown	Ureteric or biliary spasm
Skin and subcutaneous tissue disorders	Less Frequent	Serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption, allergic reactions (hypersensitivity) including skin rash have been reported.

		Risk of fixed drug eruptions and drug-induced hypersensitivity syndrome
Musculoskeletal connective tissue and bone disorder	Frequency Unknown	Muscle Rigidity
Renal and urinary disorders	Frequency Unknown	urinary retention, micturition,sweating,anti-diuretic effect
	Less Frequent	drug withdrawal syndrome
General disorders and administrative site conditions	Frequency Unknown	Hypothermia

Post-marketing experience

Risk of fixed drug eruptions and drug-induced hypersensitivity syndrome associated with the use of paracetamol containing medicines.

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 asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting form",** found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

4.9 Overdose

Paracetamol: Symptoms include nausea and vomiting. Liver damage which may be fatal may only appear after a few days.

Kidney failure has been described following acute intoxication.

In the event of overdosage, consult your 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.

Codeine: Symptoms include restlessness, excitement, respiratory depression and hypotension with circulatory failure and coma. In children convulsions may occur. The specific antagonist, naloxone hydrochloride is used to counteract the severe respiratory depression.

In the event of overdosage, consult a doctor or take the patient to the nearest hospital immediately.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A.2.8 analgesic combination.

Paracetamol has analgesic and antipyretic actions.

Codeine Phosphate is an analgesic of the opioid class. Opioid analgesic bind with stereospecific receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to it. It has been hypothesised that alterations in release of various neurotransmitters from afferent nerves sensitive to painful stimuli may be partially responsible for the analgesic effect.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

The drugs are additive and some workers suggest there may be synergy_between the constituents.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma levels occurring about 30 minutes to 2

hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate

conjugates. Less than 5 % is excreted unchanged.

The elimination half life of Paracetamol varies from about 1 to 4 hours. Plasma protein binding is negligible at usual

therapeutic doses.

Codeine Phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one

hour. Codeine is metabolised by O- and N- demethylation in the liver to morphine, and norcodeine and other metabolites.

Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

Codeine is not extensively bound to plasma proteins. The plasma half life varies from about 3 to 4 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Alcohol 90 % v/v
- Be-Tabs Red C344/TF
- Gelatin
- Magnesium Stearate
- Modified Starch

- Povidone
- Powdered Sucrose
- Purified Water
- Sodium Metabisulphite
- Starch maize
- Yellow Saffron LS2002/22

6.2 Incompatibilities

None known.

6.3 Shelf life

24 Months – 20, 100, 500, 1000 and 5000 tablets.

15 Months – Patient ready packs of different pack sizes.

6.4 Special precautions for storage

- Store at or below 25 ^{o}C.
- Protect from strong light in a well-closed container.
- Protect from moisture.
- Exposure to air should be minimum.

6.5 Nature and contents of container

Cartons with 2 X 10 tablets in push through blister packs.

Containers with 100, 500 and 1000 tablets.

Blue/green plastic buckets containing 5000 tablets.

Patient ready packs of different pack sizes.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

P/2.8/311 (S.A.)

S2 BOT 0801171 (Botswana)

NS1 90/2.8/00376 (Namibia)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 February 1996

10. DATE OF REVISON OF THE TEXT

25 August 2023