PROFESSIONAL INFORMATION:

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE:

ACURATE (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:

Paracetamol	450 mg
Doxylamine succinate	5 mg
Caffeine	30 mg
Codeine phosphate	10 mg

Sugar free

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM:

Tablets.

A round yellow, flat bevel-edged tablet with a break-line on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

ACURATE is indicated for the symptomatic relief of tension headache and other somatic pain/tension states such as neuralgia, primary dysmenorrhoea and following trauma and surgery. ACURATE calms and soothes the patient and helps allay the anxiety that can prolong or aggravate pain.

4.2 Posology and method of administration:

Adults and children 12 years and older: 2 tablets every 4 hours as needed. Do not exceed 8 tablets per day. ACURATE should not be used continuously for longer than 5 days.

DO NOT EXCEED THE RECOMMENDED DOSE.

4.3 Contraindications:

- Hypersensitivity to any of the active substances in ACURATE or to any of the excipients listed in **section 6.1**.
- Severe liver and kidney function impairment.
- Acute intermittent porphyria.
- Contraindicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, after operation on the biliary tract, acute alcoholism, head injuries and conditions in which intracranial pressure is raised. It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- Safety in pregnancy has not been established.
- In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use:

This product contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Do not use continuously for longer than 5 days without consulting your doctor.

ACURATE may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.

Dosages in excess of those recommended may cause severe liver damage.

Patients with liver or kidney disease should take paracetamol under medical supervision. The dosage in renal functional impairment must be reduced.

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

Products containing codeine should not be given for prolonged periods.

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

Paediatric population:

Not recommended for children under 12 years of age.

CY2D6 metabolism:

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7 % of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Other considerations:

Care is advised in the administration of ACURATE to patients with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urinary retention, susceptibility to angle-closure glaucoma, shock, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of cardiac arrhythmias or convulsions, and in patients with a history of drug abuse or emotional instability.

ACURATE should be taken with caution by asthmatics.

Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain

and rarely colonic obstruction. Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. See also **section 4.3** regarding contraindication of taking ACURATE with MAOIs because of the doxylamine component.

Risks from concomitant use of opioids and benzodiazepines:

Concomitant use of opioids, including codeine, and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of sedative medicines, such as benzodiazepines or related medicines, with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe codeine concomitantly with sedative medicines such as benzodiazepines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see **section 4.2**). Patients should be followed closely for signs and symptoms of respiratory depression and sedation. It is highly recommended to inform patients and their environment to be aware of these symptoms (see **section 4.5**).

Risks from concomitant use of opioids and alcohol:

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see **section 4.5**). The hazards of overdose are greater in those with non-cirrhotic alcoholic liver diseases.
Co-administration of enzyme-inducing anti-epileptic medicines may increase toxicity; doses should be reduced.

Doxylamine succinate has anticholinergic properties and should be used with care in conditions such as glaucoma and prostatic hypertrophy. The effects of atropine and tricyclic antidepressants may be enhanced by doxylamine succinate.

Doxylamine succinate may mask the symptoms of damage caused by ototoxic medicines and may affect the metabolism of medicines in the liver.

Doxylamine succinate may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers.

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with ACURATE must immediately be discontinued and appropriate treatment instituted.

4.5 Interaction with other medicines and other forms of interaction:

ACURATE may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants.

See **sections 4.3** and **4.8**.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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.

ACURATE may enhance the sedative effects of CNS depressants such as alcohol, barbiturates, anaesthetics, hypnotics, other opioid analgesics, anxiolytic sedatives, antipsychotics, tricyclic antidepressants and phenothiazines, resulting in increased CNS depression. It may also have an additive antimuscarinic action with other medicines, such as atropine and some antidepressants.

Benzodiazepines:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of an additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see **section 4.4**).

Alcohol and opioids:

The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma, and death because of an additive CNS depressant effect. Concomitant use with alcohol is not recommended (see **section 4.4**).

The hypotensive actions of diuretics and anti-hypertensive medicines 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.

The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics. Quinidine can inhibit the analgesic effect of

codeine.

Concurrent use of codeine with antidiarrhoeal and antiperistaltic medicines such as loperamide and kaolin may increase the risk of severe constipation. Concomitant use of antimuscarinics or medicines with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Codeine may delay the absorption of mexiletine and thus reduce the antidysrhythmic 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.

Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Doxylamine: Monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with these products as there is a risk of serotonin syndrome (see **section 4.3**).

Concomitant administration of pethidine and possibly other opioid analgesics to patients taking MAOIs has been associated with very severe and sometimes fatal reactions such as 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.

Incompatibilities:

Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeine-phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide.

Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two medicines, even at low moisture levels.

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 Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

The metabolism of paracetamol is possibly accelerated by carbamazepine, phenytoin, phenobarbital, primidone (also there have been isolated reports of hepatotoxicity).

4.6 Fertility, pregnancy and lactation:

The safety of ACURATE in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines:

ACURATE may lead to drowsiness and impaired concentration therefore patients should be warned against taking charge of vehicles or operating machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

4.8 Undesirable effects:

PARACETAMOL:

Immune system disorders:

Frequency unknown: Sensitivity reactions resulting in reversible skin rash or blood disorders may occur. The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by drug fever and mucosal lesions. Hypersensitivity including skin rash may occur, anaphylactic shock, angioedema.

Blood and lymphatic system disorders:

Less frequent: Thrombocytopenia

Frequency unknown: Neutropenia, pancytopenia, leucopenia, agranulocytosis

Skin and subcutaneous tissue disorders:

Less frequent: Serious skin reactions

Frequency unknown: Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see **section 4.4**)

CODEINE PHOSPHATE:

Immune system disorders:

Less frequent: Allergic reactions (itch, skin rash, facial oedema)

Metabolism and nutrition disorders:

Less frequent: Anorexia

Psychiatric disorders:

Less frequent: Hallucinations, nightmares, mental depression

Nervous system disorders:

Frequent: Drowsiness

Less frequent: Headache, dizziness, convulsions, uncontrolled muscle movements, muscle rigidity

Eye disorders:

Less frequent: Blurred or double vision

Cardiac disorders:

Less frequent: Bradycardia, palpitations

Vascular disorders:

Less frequent: Sweating, facial flushing, orthostatic hypotension, vertigo

Respiratory, thoracic and mediastinal disorders:

Less frequent: Respiratory depression, dyspnoea

Gastrointestinal disorders:

Frequent: Constipation

Less frequent: Nausea, vomiting, dry mouth, stomach cramps, pancreatitis

Renal and urinary disorders:

Less frequent: Difficulties in micturition (dysuria, increased frequency, decrease in amount)

General disorders and administration site conditions:

Less frequent: Malaise, tiredness

CAFFEINE:

Psychiatric disorders:

Frequency unknown: Restlessness, excitement or muscle tremor (with large doses), tolerance and/or psychic dependence with prolonged use

Nervous system disorders:

Frequency unknown: Headache, insomnia

Ear disorders:

Frequency unknown: Tinnitus or scintillating scotoma (with large doses)

Cardiac disorders:

Frequency unknown: Tachycardia or extrasystoles (with large doses)

Gastrointestinal disorders:

Frequency unknown: Nausea, increased gastric secretion, gastric ulceration

DOXYLAMINE SUCCINATE:

Blood and lymphatic system disorders:

Less frequent: Blood disorders

Immune system disorders:

Less frequent: Hypersensitivity reactions

Psychiatric disorders:

Less frequent: Confusion, depression, sleep disturbances

Nervous system disorders:

Frequent: Drowsiness (usually diminishes within a few days), paradoxical stimulation, headaches, psychomotor impairment

Less frequent: Extrapyramidal effects, dizziness, tremor, convulsions

Eye disorders:

Frequency unknown: Blurred vision

Cardiac disorders:

Less frequent: Palpitation, dysrhythmia

Vascular disorders:

Less frequent: Hypotension

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Thickened respiratory tract secretions

Gastrointestinal disorders:

Frequency unknown: Dry mouth, gastrointestinal disturbances

Hepato-biliary disorders:

Less frequent: Liver dysfunction

***Renal and urinary disorders*:**

Frequency unknown: Urinary retention

Post marketing:

In post-marketing experience an increased risk of abdominal pain, including pancreatitis has been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications:

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

4.9 Overdose:

Overdosage of ACURATE will produce the symptoms listed under **section 4.8** above in more severe forms.

ANTIHISTAMINES (DOXYLAMINE SUCCINATE):

Overdosage of doxylamine succinate causes sedation.

Overdosage may be fatal especially in infants and children in whom the main symptoms are central nervous 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 depression with drowsiness, coma and convulsions. Hypotension may also occur.

Treatment of antihistamine overdose is symptomatic and supportive.

PARACETAMOL:

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has the following risk factors:

Risk factors:

If the patient:

- is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other medicines that induce liver enzymes
- regularly consumes ethanol in excess of recommended amounts
- is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin may occur and the INR may increase.

Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema,

gastrointestinal bleeding and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac dysrhythmias and pancreatitis have been reported.

Management:

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour.

Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required, the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the liver unit or a hepatic specialist physician.

ACETYLCYSTEINE:

Acetylcysteine should be administered as soon as possible, preferably within 8 hours of overdosage.

IV: An initial dose of 150 mg/kg in 200 ml glucose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml glucose injection over the next 4 hours and then 100 mg/kg in 1000 ml over the next 16 hours. **The volume of intravenous fluids should be modified for children.**

ORALLY: 140 mg/kg as a 5 % solution initially, followed by a 70 mg/kg solution every 4 hours for 17 doses. Acetylcysteine is effective if administered within 8 hours of overdosage.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours 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 since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

Those whose plasma paracetamol levels are above the 'normal treatment line', should continue N-acetylcysteine 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.

Nomogram (Semi-logarithmic plot) for paracetamol plasma concentration against time after ingestion.

CODEINE PHOSPHATE:

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic medicines.

Symptoms:

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pinpoint in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

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.

5. PHARMACOLOGICAL PROPERTIES:

Pharmacological classification:

A 2.8 Analgesic combinations

5.1 Pharmacodynamic properties:

Pharmacological action:

ACURATE has analgesic, antipyretic and antihistaminic properties.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

colloidal silicon dioxide, magnesium stearate, maize starch, povidone, quinolone yellow (Cl No. 47005), sodium starch glycolate, purified talc.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

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

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

Blister packs of 20 or 100 tablets or in securitainers containing 20, 100 or 500 tablets or in a white plastic jar with a screw cap containing 1000 tablets.

6.6 Special precautions for disposal and handling:

None.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

South Africa,

2090

8. REGISTRATION NUMBERS:

Z/2.8/221

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

10 January 1992

10. DATE OF REVISION OF THE TEXT:

31 October 2024