SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

CODPARAFEN, 10 mg/200 mg/250 mg, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains

Codeine phosphate 10 mg

Ibuprofen 200 mg

Paracetamol 250 mg

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

The cap is opaque green, and the body is opaque red. “ADCO” is printed on both the cap and body. Contents of the capsule are fine white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CODPARAFEN are indicated for the relief of mild to moderate pain of inflammatory origin with or without fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Use the lowest effective dose for the shortest possible duration of treatment.

Adults and children over 12 years

One to two capsules four to six hourly and not more than six capsules per twenty-four hours.

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

Paediatric population

CODPARAFEN are not recommended for children under twelve years of age.

Method of administration

CODPARAFEN are administered orally. The capsules must be swallowed with water and not chewed.

4.3 Contraindications

- Impaired hepatic and renal function.
- Heart failure.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including CODPARAFEN.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Cardiovascular disease.

- Hypersensitivity to any of the active ingredients.
- Contraindicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, after operations on the biliary tract, acute alcoholism, convulsive disorders, 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.
- Contra-indicated in patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment.
- CODPARAFEN are contraindicated in patients with a history of hypersensitivity reactions to aspirin or other NSAID's, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.
- Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios / foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

The safety of continuous administration of CODPARAFEN has not been established for a period greater than four weeks.

Codeine phosphate

- **Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction.**
- Codeine phosphate should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, asthma, impaired liver or kidney function, prostatic hyperplasia, shock, hypotension, inflammatory or obstructive bowel disorders or myasthenia gravis.

- The dosage should be reduced in elderly and debilitated patients.

Ibuprofen

- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with CODPARAFEN therapy. In view of CODPARAFEN' inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including CODPARAFEN, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of CODPARAFEN, in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving CODPARAFEN, treatment with CODPARAFEN should be stopped.
- CODPARAFEN should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. CODPARAFEN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as CODPARAFEN. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash,

lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue CODPARAFEN and evaluate the patient immediately.

- Use of NSAIDs including CODPARAFEN during the third trimester of pregnancy, may result in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased (see section 4.6).
- CODPARAFEN should be used with caution in patients with infection since symptoms such as fever and inflammation may be masked.
- Other precautions to be observed include administration to patients with haemorrhagic disorders, asthma, a history of hypersensitivity reactions to aspirin or other nonsteroidal anti-inflammatory medications and impaired renal, hepatic or cardiac function. Should be used with caution in the elderly.
- Caution is advised in those patients who are receiving coumarin anticoagulants (see section 4.5).
- Foetal Toxicity: Limit use of NSAIDs, including CODPARAFEN, between 20 to 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs in women at around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus.

  If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit CODPARAFEN use to the lowest effective dose and shortest duration possible. Consider

ultrasound monitoring of amniotic fluid if CODPARAFEN treatment extends beyond 48 hours. Discontinue CODPARAFEN if oligohydramnios occurs and follow up according to clinical practice (see section 4.3 and 4.6).

Paracetamol

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.

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

4.5 Interactions with other medicines and other forms of interaction

Codeine phosphate

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

Ibuprofen

- Lithium, methotrexate and cardiac glycosides: increased plasma concentrations may result.
- ACE inhibitors, cyclosporin, tacrolimus, or diuretics: concurrent administration may increase the risk of nephrotoxicity.
- Effects on renal function may lead to reduced excretion of some medicines.
- Antihypertensives: the antihypertensive effects of some antihypertensives, including ACE inhibitors, beta blockers, and diuretics may be reduced. There may also be an increased risk of hyperkalaemia with ACE inhibitors and potassium-sparing diuretics.

- Quinolones: convulsions may occur.
- Moclobemide: the effects of NSAID's might be enhanced.
- Phenytoin and sulphonylurea antidiabetics: effects may be enhanced.
- Mifepristone: it is advised that NSAID's should be avoided 8 to 12 hours after mifepristone use, because of a theoretical risk that these prostaglandin synthetase inhibitors may alter the efficacy of mifepristone.
- Zidovudine: may increase the risk of haemotoxicity.
- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.
- Alcohol, bisphosphonates or oxpentifylline: possible increased risk of NSAID associated gastrointestinal bleeding and ulceration.
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).
- Anti-coagulants: CODPARAFEN may enhance the effects of anti-coagulants such as warfarin.
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

CODPARAFEN are not recommended for use by pregnant or breastfeeding women (see section 4.3). Use of non-steroidal anti-inflammatory drugs during the third trimester of pregnancy, may result in persistent pulmonary hypertension of the new-born.

Use of NSAIDs, including CODPARAFEN, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, the use of CODPARAFEN dose and duration between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation

and later in pregnancy (see sections 4.3 and 4.4).

The onset of labour may be delayed and its duration increased.

Fertility

No data on male and female fertility are available

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation. This medicine can impair cognitive function and can affect a patient's ability to drive safely. Patients should be advised that they do not engage in the above activities until they are aware of the measure to which CODPARAFEN affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

b. Tabulated summary of adverse reactions

Codeine phosphate

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Psychiatric disorders	Frequency unknown	Changes of mood, hallucinations.
Nervous system disorders	Frequency unknown	Drowsiness, dizziness, headache, confusion, restlessness, vertigo, raised intracranial pressure.

Eye disorders	Frequency unknown	Miosis.
Cardiac disorders	Frequency unknown	Bradycardia, tachycardia, palpitations.
Vascular disorders	Frequency unknown	Orthostatic hypotension.
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, constipation, dry mouth.
Skin and subcutaneous tissue disorders	Frequency unknown	Sweating and facial flushing. Reactions such as urticaria, and pruritus.
Renal and urinary disorders	Frequency unknown	Micturition may be difficult and there may be ureteric or biliary spasm.
Reproductive system and breast disorders	Frequency unknown	Decreased libido or potency.
General disorders and administrative site conditions	Frequency unknown	Hypothermia.

Ibuprofen

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**

Blood and the lymphatic system disorders	Less frequent	Anaemias, thrombocytopenia, neutropenia, eosinophilia, agranulocytosis.
	Frequency unknown	Reversible inhibition of platelet aggregation.
Immune system disorders *(Hypersensitivity reactions include)*	Frequent	Rashes.
	Less frequent	Angioedema, bronchospasm, hepatotoxicity and aseptic meningitis.
	Frequency unknown	Fever.
Nervous system disorders	Frequent	Dizziness.
	Less frequent	Nervousness, depression, drowsiness, insomnia.
	Frequency unknown	Headache, vertigo.
Eye disorders	Less frequent	Visual disturbances.
Ear and labyrinth disorders	Less frequent	Tinnitus.
Cardiac disorders	Less frequent	Oedema, hypertension, cardiac failure.
Gastrointestinal disorders	Frequent	Nausea and abdominal pain.
	Less frequent	Vomiting, diarrhoea, flatulence, constipation, dyspepsia, peptic ulcers, perforation or gastrointestinal bleeding,

		sometimes fatal, melaena, haematemesis, ulcerative stomatitis, gastritis.
	Frequency unknown	Exacerbation of colitis and Crohn's disease, gastrointestinal discomfort.
Skin and subcutaneous tissue disorders	Less frequent	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).
Renal and urinary disorders	Less frequent	Renal failure.
	Frequency unknown	Interstitial nephritis, nephrotic syndrome

Paracetamol

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and the lymphatic system disorders	Less frequent	Haematological reactions including thrombocytopenia, leukopenia, pancytopenia, neutropenia, agranulocytosis.
Immune system disorders	Less frequent	Hypersensitivity reactions.
Gastrointestinal disorders	Frequency unknown	Pancreatitis.

Skin and subcutaneous tissue disorders	Less frequent	Skin rashes. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions.

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 professionals 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

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. 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 stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

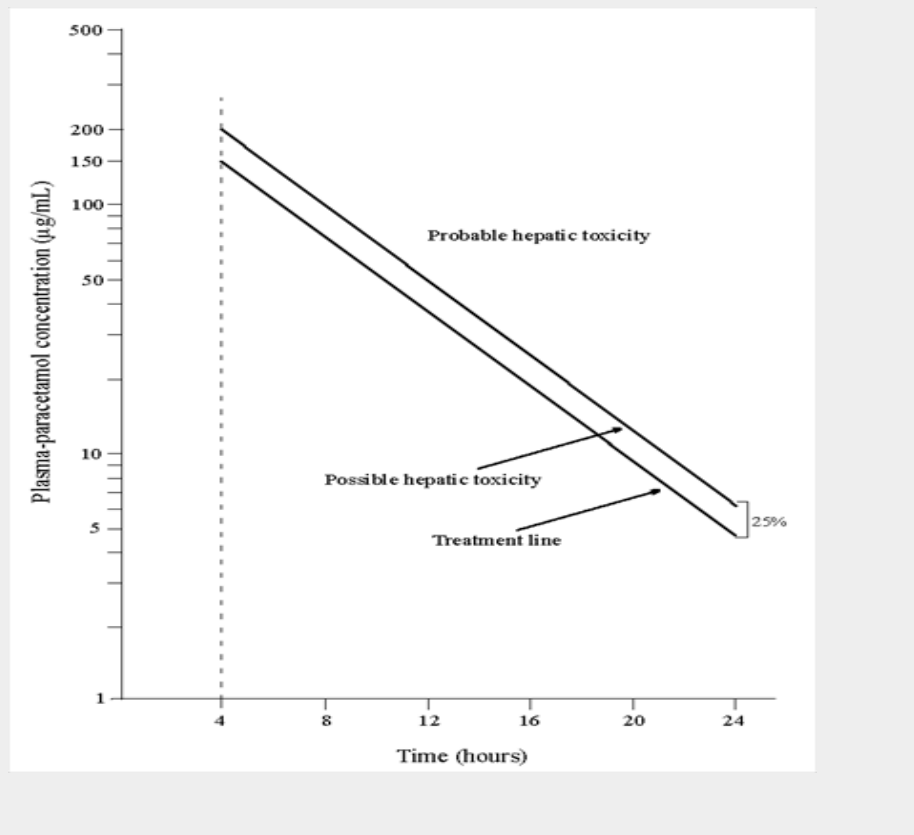
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg 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 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 since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion. (Reference: Martindale).



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.

Codeine phosphate

Symptoms of overdosage include excitement and, in children, convulsions may occur. Large doses produce respiratory depression.

Treatment of overdosage is symptomatic and supportive.

Ibuprofen

The most likely symptoms of overdosage are nausea, vomiting and tinnitus.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 2.8 Analgesic combinations

CODPARAFEN have an analgesic, anti-inflammatory and anti-pyretic action.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Colloidal silica

Magnesium stearate

Maize starch

Potassium sorbate.

Capsule shell

Opaque Green Cap

Opaque Red Body

Printing ink

Capsule shell colourants

Brilliant blue FCF, E 133 (C.I. 42090)

Erythrosine, E 127 (C.I. 45430)

Quinoline yellow, E 104 (C.I. 47005)

Sunset yellow, E 110 (C.I. 15985)

Titanium dioxide, E 171 (C.I. 77891)

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 well-closed container.

6.5 Nature and contents of container

- A white high-density polypropylene (HDPP) securitainers with a low-density polyethylene (LDPE) snap on lid or a white high density polyethylene container with a high-density polyethylene (HDPE) screw cap containing 30 capsules.
- Push through clear PVC and aluminium blister packs of 10 capsules in unit cartons of 10, 30, 60 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

Customer Care: 0860 ADCOCK 232625

8. REGISTRATION NUMBER

57/2.8/0731

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT

14 June 2023