SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

ADCO-DOL

Strength

Codeine phosphate	10 mg
Doxylamine succinate	5 mg
Paracetamol	450 mg
Caffeine	45 mg

Pharmaceutical form

Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Codeine phosphate	10 mg
Doxylamine succinate	5 mg
Paracetamol	450 mg
Caffeine	45 mg

Colour Sunset Yellow FCF Lake (Pigment blend orange P.B 5691) CI Number: 15985

Sugar free

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablets

Yellow, circular, flat tablet, scored on one side only, and embossed with "ADCO" above and "DOL" below the score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO-DOL tablets for the symptomatic relief of mild to moderate pain, pain associated with tension, and fever in adults.

4.2 Posology and method of administration

Adults and children over 12 years:

One or two tablets repeated four hourly if necessary.

Do not exceed eight tablets per day.

DO NOT EXCEED THE RECOMMENDED DOSE.

Paediatric population

ADCO-DOL should not be used in children under 12 years.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to codeine phosphate, doxylamine succinate, paracetamol, caffeine anhydrous or any of the excipients listed in section 6.1.
- Severe liver function impairment (see section 4.4).
- Acute intermittent porphyria.
- ADCO-DOL tablets should not be given to children under 12 years of age.
- In women who are breastfeeding (see section 4.6).
- In women who are pregnant (see section 4.6).
- Contraindicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- Contraindicated after operations on the biliary tract
- Contraindicated in the presence of 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 fourteen days of stopping such treatment is contraindicated, as there is a risk of serotonin syndrome (see section 4.5).
- Patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers (see section 4.4 and 4.6).
- Severe hepatocellular insufficiency.
- ADCO-DOL should not be used at all in children (0 - 18 years of age) who undergo tonsillectomy or adenoidectomy surgery for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

4.4 Special warnings and precautions for use

ADCO-DOL 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.

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

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

Do not take concurrently with any other paracetamol or codeine containing compounds.

Children with compromised respiratory function: Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

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

Paracetamol dosages in excess of those recommended may cause severe liver damage.

Patients suffering from liver or kidney disease should take paracetamol under medical supervision.

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction.

Care is advised in the administration of ADCO-DOL 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 dysrhythmias or convulsions, and in patients with a history of drug abuse or emotional instability.

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.

Patients who have had a cholecystectomy should be treated with caution. The contraction of the sphincter of Oddi can cause symptoms resembling those of myocardial infarction or intensify the symptoms in patients with pancreatitis.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence develops with prolonged use of high doses with withdrawal symptoms after sudden discontinuation of the medicine. Cross tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission).

Administration must be discontinued gradually after prolonged treatments.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults, and in patients with a history of drug and/or alcohol abuse.

Opioid use disorder (abuse and dependence): A cautious approach is required for the use of opioids, such as codeine, in patients with a history of mental health disorders.

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of ADCO-DOL may result in overdose and/or death.

Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

Withdrawal symptoms, such as restlessness and irritability may occur once the medicine is stopped.

Increased risk of addiction in patients with personal or family history of substance abuse or mental health disorders.

Opioid-induced hyperalgesia (OIH): 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 quickly 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 ordinarily non-painful stimuli (allodynia).

Excessive intake of caffeine (products with caffeine e.g. coffee, tea, foods, other medicines and beverages) should be avoided while taking ADCO-DOL in patients with a history of peptic ulceration.

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 ADCO-DOL with MAOIs because of the doxylamine component.

ADCO-DOL must be administered with caution in certain patients, such as those with hypotension.

ADCO-DOL must be administered with caution in certain patients, such as those who present impaired cardiac, hepatic or renal function, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, gallbladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

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. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Caution is advised in patients with:

- Anxiety disorders (risk of enhancement).
- Dysrhythmia (risk of tachycardia or extra systoles enhancement).

ADCO-DOL should be used upon medical advice in patients with:

- Mild-to-moderate hepatocellular insufficiency
- Severe renal insufficiency
- Chronic alcohol use including recent cessation of alcohol intake
- Low glutathione reserves
- Glucose-6-phosphate-dehydrogenase deficiency
- Gilbert´s syndrome

ADCO-DOL should only be used after careful risk-benefit assessment in case of:

- Opioid dependence.
- Chronic constipation.
- Impaired consciousness.
- Compromised respiratory function (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airway disease.

Elderly people may be more sensitive to the effects of ADCO-DOL, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age-related kidney impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.

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.

Coadministration of enzyme-inducing antiepileptic medications may increase toxicity; doses should be reduced.

Monitoring after prolonged use should include blood count, liver function and renal function.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the medicine. In such cases the analgesic should not continue to be taken without medical advice.

CY2D6 metabolism

Codeine is metabolised by the liver 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. 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.

Large doses may precipitate fits in epileptics.

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), Drug reaction with eosinophilia and systemic symptoms (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 ADCO-DOL must immediately be discontinued and appropriate treatment instituted.

ADCO-DOL contains Colour Sunset Yellow FCF Lake (Pigment blend orange P.B 5691) CI Number: 15985; Colour Quinoline yellow Lake (IH 661541300) CI Number: 47005; Colour Quinoline yellow WS (QY 800744) CI Number: 47005. This may cause allergic reactions.

4.5 Interactions with other medicines and other forms of interactions

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

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

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. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes, such as certain antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, other opioid analgesics, anxiolytic and 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. Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety medicine or other CNS depressants (including alcohol) concomitantly with this codeine containing medicine may exhibit additive CNS depression.

Benzodiazepines

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increase the risk of sedation, respiratory depression, coma and death because of 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 additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

Morphine agonists-antagonists

Concomitant use of codeine with a partial agonist (e.g. buprenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

CYP2D6 inhibitors

Codeine is metabolized by the liver enzymeCYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine.
Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers

Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Caffeine may antagonise the sedative effect of other medicines (e.g. barbiturates, antihistamines). Caffeine reduces excretion of theophylline.

The concomitant intake of gyrase inhibitors of the quinolone carbonic acid type (e.g., enoxacin, ciprofloxacin) can delay the elimination of caffeine and its degradation product paraxanthine. CYP1A2 inhibitors (e.g., oral contraceptives, cimetidine, fluvoxamine, disulfiram, mexiletine) may reduce the caffeine metabolism in the liver.

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 medicines 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 medications 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 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.

Doxylamine succinate may enhance the sedative effect of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers.
Doxylamine may decrease emetic response to apomorphine.

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 and 4.4).

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

Pregnancy

ADCO-DOL should not be used during pregnancy (see section 4.3).

Reported epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

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 physical dependence in the foetus leading to withdrawal symptoms in the neonate.

Use of opioid analgesia during labour may cause respiratory depression in the neonate, especially the premature neonate. These medicines should not be given during the delivery of a premature baby.

Breastfeeding

ADCO-DOL should not be used during breastfeeding (see section 4.3).

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Codeine should not be used during breastfeeding.

At normal therapeutic doses codeine and its active metabolites 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 CYP2D6, higher levels of the active metabolites 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 (see section 4.3 and 4.4).

4.7 Effects on ability to drive and use machines

Patients should be warned against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

4.8 Undesirable effects

Undesirable Effects of the Combination Product (ADCO-DOL)

Blood and the lymphatic system disorders	
Less frequent	Thrombocytopaenia, leucopaenia, pancytopaenia, neutropaenia, agranulocytosis.
Frequency unknown	Eosinophilia.
Immune system disorders	

Less frequent	Hypersensitivity reactions.
Frequency unknown	Bronchospasm, angioedema, anuria, allergy, anaphylaxis
Psychiatric disorders	
Frequent	Drowsiness, confusion
Frequency unknown	Psychomotor Impairment, extrapyramidal effects, sleep disturbances, decreased libido.
Nervous system disorders	
Frequent	CNS depression, drowsiness (usually diminished within a few days), headache, paradoxical stimulation (especially in children).
Less Frequent	Tremor, paraesthesia, dizziness, convulsions, uncontrolled muscle movements.
Frequency Unknown	Incoordination, photosensitivity, restlessness, excitement, muscle tremor, CNS stimulation, deepening coma, dizziness, raised intracranial pressure.
Eye disorders	
Frequent	Blurred vision.
Frequency Unknown	Scintillating scotoma, miosis
Ear and labyrinth disorders	
Less Frequent	Tinnitus, vertigo.
Cardiac disorders	
Less Frequent	Tachycardia, hypotension, palpitations, dysrhythmias.
Respiratory, thoracic and mediastinal disorders	
Less Frequent	Thickened respiratory tract, secretions, respiratory depression.
Frequency unknown	Tightness of the chest, dyspnoea.
Hepato-biliary disorders	
Less Frequent	Jaundice.
Frequency unknown	Porphyria symptoms may be exacerbated.
Gastrointestinal disorders	
Frequent	Dry mouth, gastrointestinal disorders, nausea, vomiting, diarrhoea,

	constipation.
Less Frequent	Increased risk of abdominal pain, pancreatitis.
Frequency unknown	Epigastric pain, gastric ulceration
Skin and subcutaneous tissue disorders	
Less frequent	Reversible skin rash.
Frequency unknown	Erythema, urticaria, mucosal lesions, risk of fixed drug eruptions and drug- induced hypersensitivity syndrome. Rashes, urticaria, purpura, erythema multiforme, exfoliative or bullous dermatitis, pruritus, urticaria.
Musculoskeletal, connective tissue and bone disorders	
Frequency unknown	Myalgia, muscle rigidity
Renal and urinary disorders	
Frequent	Urinary retention
Frequency unknown	Difficulty in micturition, ureteric or biliary spasm, antidiuretic effect
Reproductive system and breast disorders	
Less Frequent	Decreased potency
General disorders and administrative site conditions	
Less Frequent	Malaise, Tiredness
Frequency unknown	Heaviness of hands, sweating, hair loss, facial flushing, hyperthermia hypothermia.

Undesirable Effects by Active Pharmaceutical Ingredient (API)

	Paracetamol	**Doxylamine succinate**	**Caffeine**	**Codeine Phophate**
Blood and the lymphatic system disorders				
Less frequent	Thrombocytopaenia Leucopaenia Pancytopaenia Neutropaenia	Thrombocytopaenia Leucopaenia Agranulocytosis Haemolytic anaemia		

	Agranulocytosis			
Frequency unknown		Eosinophilia		
Immune system disorders				
Less frequent	Hypersensitivity reactions	Hypersensitivity reactions		Allergic Reactions
Frequency unknown	Anaphylactic shock Angioedema	Bronchospasm Angioedema Anuria Allergy Anaphylaxis		
Psychiatric disorders				
Frequent				Drowsiness Confusion
Frequency unknown		Psychomotor Impairment Extrapyramidal effects Sleep disturbances	Insomnia	Restlessness Changes in mood Euphoria Decreased libido Hallucinations
Nervous system disorders				
Frequent		CNS depression Drowsiness (usually diminished within a few days) Headache Paradoxical stimulation (especially in children)	CNS stimulation Headache Anxiety Restlessness Dizziness Tremor	Drowsiness
Less Frequent		Dizziness	Headache	Dizziness

		Tremor Muscles twitching Convulsions Paraesthesia		Headache Convulsions Uncontrolled muscle movements
Frequency Unknown		Slight drowsiness to deep sleep Lassitude Incoordination Photosensitivity	Restlessness Excitement Muscle Tremor CNS stimulation Anxiety Dizziness	Deepening coma Dizziness Headache Raised intracranial pressure
Eye disorders				
Frequent		Blurred vision		
Less Frequent				Blurred or double vision
Frequency Unknown			Scintillating scotoma	Miosis
Ear and labyrinth disorders				
Less Frequent		Tinnitus		Vertigo
Frequency Unknown			Tinnitus	
Cardiac disorders				
Less Frequent		Tachycardia Hypotension Palpitations Dysrhythmias		Orthostatic hypotension
Frequency Unknown			Tachycardia Extrasystole Palpitations	Hypotension Circulatory failure Tachycardia
Respiratory, thoracic and mediastinal disorders				
Less Frequent		Thickened		Respiratory

		respiratory tract secretions		depression
Frequency unknown		Tightness of the chest and tingling		Dyspnoea
Hepato-biliary disorders				
Less Frequent		Jaundice		
Frequency unknown		Porphyria symptoms may be exacerbated		
Gastrointestinal disorders				
Frequent		Dry mouth Gastrointestinal disorders Nausea Vomiting Diarrhoea		Nausea Vomiting Constipation
Less Frequent			Nausea	Dry mouth Increased risk of abdominal pain, including pancreatitis
Frequency unknown	Pancreatitis	Constipation Increased gastric reflux Epigastric pain	Gastric Ulceration	Stomach cramps
Skin and subcutaneous tissue disorders				
Less frequent	Reversible skin rash			
Frequency unknown	Erythema Urticaria Mucosal	Rashes Urticaria		Pruritus Urticaria

	lesions Risk of fixed drug eruptions and drug-induced hypersensitivity syndrome	Purpura Erythema multiforme Exfoliative or bullous dermatitis		
Musculoskeletal, connective tissue and bone disorders				
Frequency unknown		Myalgia		Muscle rigidity
Renal and urinary disorders				
Frequent		Urinary retention		
Frequency unknown		Difficulty in micturition		Difficulty in micturition Ureteric or biliary spasm Antidiuretic effect
Reproductive system and breast disorders				
Less Frequent				Decreased potency
General disorders and administrative site conditions				
Less Frequent				Malaise Tiredness
Frequency unknown		Heaviness of hands Sweating Hair loss		Sweating Facial flushing Hyperthermia Hypothermia

Post-marketing experience:

Less frequent: 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) or via the eReporting platform (who-umc.org) found on the SAHPRA website. Alternatively use the **"Adverse Drug Reactions (ADR)/Product Quality Problem Reporting Form**" found online under SAHPRA's publications:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

One may also report to Adcock Ingram Limited using the following email:

Adcock.AEReports@adcock.com

4.9 Overdose

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 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 dysrhythmias 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** 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.
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.

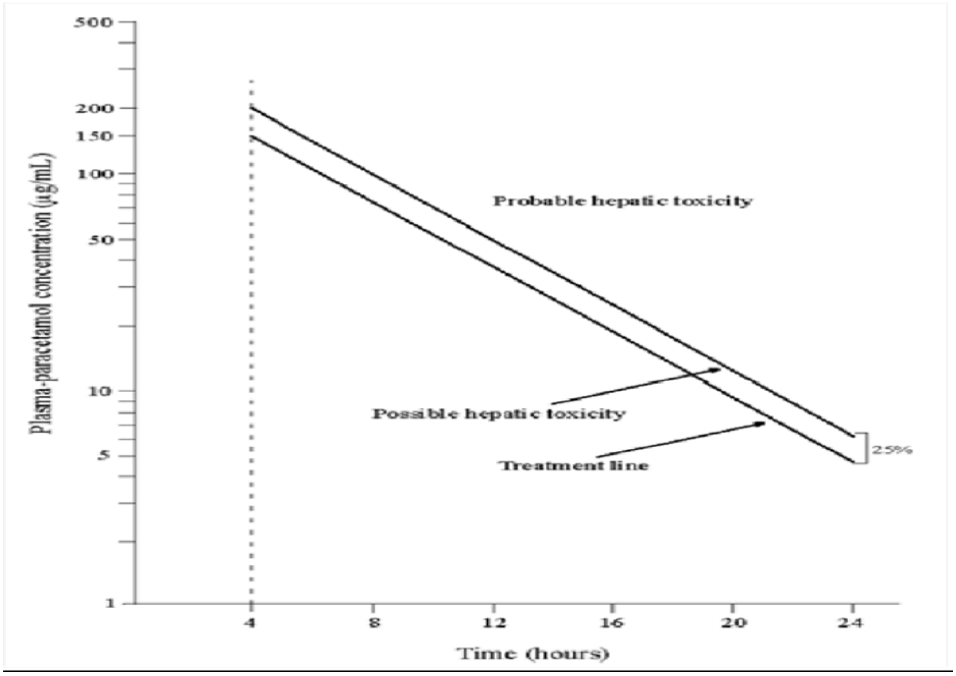


Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion. (Reference: Martindale 37th Edition)

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 system 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 system depression with drowsiness, coma and convulsions. Hypotension may also occur. Treatment of antihistamine overdose is symptomatic and supportive.

Codeine phosphate:

Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops.

In acute poisoning by an opioid taken by mouth the stomach should be emptied. A laxative may be given to aid peristalsis. Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses of opioid analgesics.

Caffeine: Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac dysrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, metabolic acidosis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Elimination may be enhanced by repeated oral doses of activated charcoal. An osmotic laxative may also be given. Treatment is symptomatic and supportive. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium under ECG monitoring. In the non-asthmatic patient extreme tachycardia, hypokalaemia, and hyperglycaemia may be reversed by beta blockers. Convulsions should be controlled by the intravenous administration of diazepam. Charcoal haemoperfusion or haemodialysis may be required.

5. PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: Anilides, Paracetamol combinations ATC Code: NO2B E51.

Mechanism of action

ADCO-DOL tablets have antipyretic, analgesic and antihistaminic properties.

Paracetamol is an effective, well-documented analgesic preparation.

Codeine is a proven analgesic medicine, which has a suggested central action.

Doxylamine succinate is an ethanolamine type antihistamine with mild sedative, anti-allergic and anti-emetic properties. Because of its sedative action, it reduces the psychic tension component of tension headache and other somatic pain/tension states.

Caffeine has a mild stimulant effect on the cerebral cortex and relieves fatigue.

5.2 Pharmacokinetic properties

Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration, the effects start within 15 to 30 minutes and peak within one hour. In humans 60 - 80 % of doxylamine given has been recovered in urine at 24 hours post-dose.

The bioavailability of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately.

Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O-demethylation leading to morphine, N-demethylation to norcodeine and both O- and N-demethylation to normorphine.

Morphine and norcodeine are further transformed to glucuronide conjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48 hours (84,4 ± 15,9 %).

The O-demethylation of codeine to morphine is catalyzed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine. Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colour sunset FCF lake,

Colour quinoline yellow lake,

Colour quinoline yellow WS,

Gelatin,

Maize starch,

Magnesium stearate,

Purified talc,

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from light and moisture.

Do not remove the blister pack from the outer carton until required for use.

6.5 Nature and contents of container

Blister packs consisting of PVC film and aluminium foil.

White propylene securitainer with white LDPE cap.

Blister packs of 20, 40 tablets Securitainers of 20 tablets.

Not all pack types and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

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Midrand, 1685

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Bryanston, 2021

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PROFESSIONAL INFORMATION

8. REGISTRATION NUMBER:

U/2.8/159

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

16 August 1988

10. DATE OF REVISION OF THE TEXT

10 April 2026

Namibia: NSI 90/2.8/0083
Botswana: B9300175 S3