

SCHEDULING STATUS:

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PROPRIETARY NAME AND DOSAGE FORM:

COMPRAL® PAIN TABLETS (TABLET)

COMPOSITION:

Each tablet contains:

Paracetamol	100 mg
Aspirin	400 mg
Caffeine anhydrous	30 mg

List of excipients: Acacia, starch corn, purified talc, hydrogenated cottonseed oil, sodium lauryl sulphate, colloidal silicon dioxide, microcrystalline cellulose, purified water

Sugar free

PHARMACOLOGICAL CLASSIFICATION:

A 2.8 Analgesic combinations

PHARMACOLOGICAL ACTION:

COMPRAL PAIN TABLETS have analgesic, anti-inflammatory and antipyretic actions. They inhibit the biosynthesis of prostaglandins.

INDICATIONS:

COMPRAL PAIN TABLETS are effective for the relief of pain of mild to moderate intensity and is also indicated in a wide variety of febrile conditions.

CONTRAINDICATIONS:

Patients with haemophilia, severe renal impairment or patients receiving oral anticoagulant therapy.

Intolerance or hypersensitivity to aspirin or other NSAIDs, paracetamol, caffeine or to any of the ingredients of **COMPRAL PAIN TABLETS**.

Active or history of recurrent ulcer/haemorrhage/perforations.

Heart failure

History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including **COMPRAL PAIN TABLETS**.

Not for use in children and adolescents under 18 years of age.

WARNINGS AND SPECIAL PRECAUTIONS:

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.

Aspirin has been implicated in Reye's Syndrome, a rare but serious illness, in children and teenagers with chickenpox or influenza. A doctor should be consulted before aspirin is used in such patients.

COMPRAL PAIN TABLETS should not be used in children and adolescents under 18 years of age.

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 **COMPRAL PAIN TABLETS** therapy. In view of the **COMPRAL PAIN TABLETS** 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 **COMPRAL PAIN TABLETS**, 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 **COMPRAL PAIN TABLETS**, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving **COMPRAL PAIN TABLETS**, treatment with **COMPRAL PAIN TABLETS** should be stopped.

COMPRAL PAIN TABLETS 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. **COMPRAL PAIN TABLETS** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Regular use of NSAIDs such as **COMPRAL PAIN TABLETS** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Patients suffering from liver or kidney disease should take **COMPRAL PAIN TABLETS** under medical supervision.

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

Consult a doctor if no relief is obtained from the recommended dosage.

Excessive and prolonged use of this medicine may be dangerous.

Store in a safe place out of reach of children.

INTERACTIONS

Aspirin

Aspirin may enhance the activity of oral antidiabetic preparations and sulphonamides. Aspirin diminishes the effects of antigout preparations such as probenecid and sulphinyprazone.

Barbiturates and other sedatives may mask the respiratory symptoms of aspirin overdose and have been reported to enhance its toxicity

NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs)

Anti-coagulants: COMPRAL PAIN TABLETS may enhance the effects of anti-coagulants such as warfarin.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy

Not to be taken during the first and third trimesters of pregnancy except under the advice and supervision of a medical doctor.

DOSAGE AND DIRECTIONS FOR USE:

DO NOT EXCEED THE RECOMMENDED DOSE

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

Adults: 1 to 2 tablets, 4 hourly.

Not more than 4 doses in 24 hours.

Not for use in children and adolescents under 18 years of age.

SIDE EFFECTS

Paracetamol:

Skin rashes and other allergic reactions may occur. The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions. The use of paracetamol has been associated with the occurrence of neutropenia, pancytopenia and leucopenia.

Aspirin:

Dizziness or irritation of the gastric mucosa and resultant dyspepsia, haematemesis, and melaena may occur in some cases. Some persons, especially asthmatics exhibit notable sensitivity to aspirin which may include skin eruptions, paroxysmal bronchospasm and dyspnoea.

Prolonged use of high doses may lead to anaemia, blood dyscrasias, gastrointestinal haemorrhage, peptic ulceration and renal papillary necrosis.

Cardiac disorders:

Oedema, hypertension and cardiac failure.

Gastrointestinal system disorders:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Skin and subcutaneous tissue disorders:

Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Prompt treatment is essential. In the event of an overdose, 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 arrhythmias have been reported.

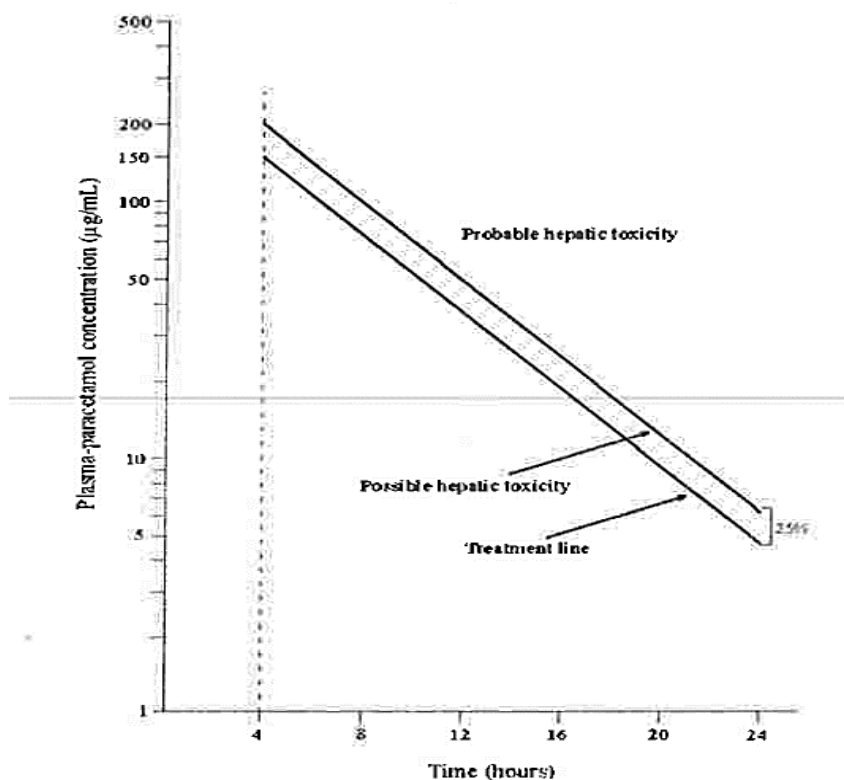
Treatment for paracetamol overdosage:

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 stuporose 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 overdose. 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.



Source: Martindale: The Complete Drug Reference - 37th Edition.

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.

Aspirin:

Symptoms include dizziness, tinnitus, sweating, nausea, vomiting, mental confusion, hyperventilation, respiratory alkalosis, metabolic acidosis, ketosis and depression of the central nervous system. In children serious signs of overdosage may develop rapidly.

IDENTIFICATION:

White, scored, bevel-edged tablets with the word "COMPRAL" imprinted on one side.

PRESENTATION:

Polypaper strips of 2 tablets packed in a display carton or a display board of 48 x 2's,

ALU/PVC/PVDC blister packs containing 12, 24, 36 or 72 tablets,

ALU/ALU blister packs of 2 tablets, packed into a display carton of 50 x 2's

ALU/ALU blister packs of 6 tablets per strip packed into cardboard cartons of 12, 24, 48 and 96 tablets,

PP/HDPE tracer packs of 50 and 100 tablets.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a well-closed container. Exposure to air should be kept to a minimum.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

B/2.8/1147

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF
REGISTRATION:**

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