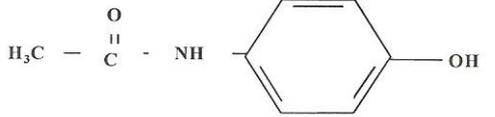
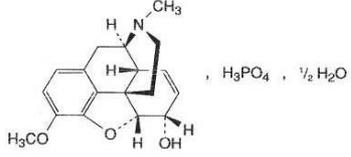


Panadeine Extra

PRODUCT INFORMATION

NAME OF MEDICINE

Active ingredients	Chemical structure	CAS Registry Number
Paracetamol		103-90-2
Codeine Phosphate		41444-62-6

DESCRIPTION

FORMULATION

Active Ingredients

Paracetamol 500 mg

Codeine phosphate 15 mg

Excipients

Starch - maize, talc - purified, stearic acid, titanium dioxide, povidone, starch pregelatinised maize, potassium sorbate, magnesium stearate.

Contains no sugar, lactose or wheat starch.

PHARMACOLOGY

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. It does not possess anti-inflammatory activity. It is given by mouth or rectally for mild to moderate pain and fever.

Codeine phosphate is an opioid analgesic which binds with stereospecific receptors at many sites within the central nervous system. It alters processes affecting both the perception of pain and the emotional response to pain. Codeine has about one-sixth of the analgesic activity of morphine.

After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma levels occur 10 to 60 minutes after administration.

Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45 to 55%) or sulfate (20 to 30%).

A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant. Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85 to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 3 hours. Food intake delays paracetamol absorption.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations are reached one hour after oral administration.

Codeine is metabolised in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney within 24 hours. The metabolites are mainly conjugates with glucuronic acid.

Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

The plasma half-life varies between three and four hours after oral administration.

CLINICAL TRIALS

Adverse event data from clinical trials of codeine are sparse and are based on higher doses of codeine than that contained in this product. These data are unreliable for determining the nature and frequency of adverse reactions at dose of codeine contained in this product.

INDICATIONS

For the temporary relief of pain and discomfort associated with:

▪ Headache	▪ Arthritis
▪ Migraine headache	▪ Toothache
▪ Tension headache	▪ Neuralgia
▪ Period pain	▪ Cold & flu symptoms
▪ Musculoskeletal pain	▪ Dental procedures
▪ Muscle ache	▪ Sore throat

CONTRAINDICATIONS

- Previous history of hypersensitivity to paracetamol, codeine, opioid analgesics, or excipients.
- Active alcoholism.
- Acute respiratory depression.
- In mothers who are breastfeeding
- In children under the age of 18 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see Pharmacology).
- Those who are known to be CYP2D6 ultra-rapid metabolisers. If the patient is an extensive or ultra-rapid CYP2D6 metaboliser there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses.

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.

PRECAUTIONS

Adults: Not to be taken for more than three days unless on the advice of a doctor. Prolonged or excessive consumption of codeine can result in dependence.

Panadeine is for the relief of minor and temporary ailments and should be used strictly as directed. If symptoms persist or worsen, medical advice must be sought.

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking paracetamol. Underlying liver disease increasing the risk of paracetamol-related liver injury.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

In patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis.

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve.

Patients taking the following medications should consult a physician prior to taking this product (see *Drug Interactions*).

- Metoclopramide
- Domperidone
- Central nervous system depressants, including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressant and phenothiazine
- Monoamine oxidase inhibitors (MAOI)

Patients should be advised not to drive or operate machinery if affected by dizziness or drowsiness.

Use in Pregnancy & Lactation

Pregnancy

Category A - Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Use during pregnancy should be avoided unless advised by a doctor. This includes maternal use during labor because of the potential of respiratory depression in the neonate.

The safety of paracetamol and codeine during pregnancy has not been established relative to possible adverse effects on foetal development.

Lactation

Codeine-containing products must not be used while breastfeeding.

In nursing mothers, who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia and difficulty breastfeeding or breathing. In severe cases respiratory depression and death can occur.

Use in Children

Do not use in children under 18 years of age.

INTERACTIONS WITH OTHER MEDICINES

Paracetamol

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.

Paracetamol absorption is increased by drugs which increase gastric emptying, e.g. metoclopramide, and decreased by drugs which decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations. The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant drugs.

Codeine

It is possible that interactions could occur between drugs that can inhibit CYP2D6 (such as quinidine, phenothiazines and antipsychotic agents) and codeine.

Codeine potentiates the central depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

Opiate analgesics may interact with monoamine oxidase inhibitors (MOAIs) and result in serotonin syndrome.

Codeine may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility.

ADVERSE EFFECTS

Undesirable effects depend on dose and individual patient metabolism. Some patients are more like to experience undesirable effects because they rapidly convert codeine to morphine (see Pharmacology).

Post Marketing Data

Paracetamol

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

The following convention has been utilised for the classification of undesirable effects: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data and are considered to be very rare.

Body System	Undesirable Effect
Blood and lymphatic system disorders	<i>Thrombocytopaenia</i>
Immune System disorders	<i>Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema, and Stevens Johnson syndrome</i>
Respiratory, thoracic and mediastinal disorders	<i>Bronchospasm, especially in patients sensitive to aspirin and other NSAIDs.</i>
Hepatobiliary disorders	<i>Hepatic dysfunction</i>

Reports of adverse reactions to paracetamol are rare. Although the following adverse reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted: dyspepsia and nausea.

Codeine

Adverse reactions identified during post-marketing use are listed below by MedDRA System Organ Class. The frequency of these reactions is not known.

Body System	Undesirable Effect
Psychiatric disorders	<i>Drug dependency can occur after prolonged use of codeine at higher doses</i>
Gastrointestinal Disorder	<i>Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of</i>

	<i>cholecystectomy</i>
Nervous System Disorder	<i>Dizziness, worsening of headache with prolonged use, drowsiness.</i>
Skin and Subcutaneous Tissue Disorder	<i>Pruritus, sweating</i>

Very rarely, skin rashes may occur in patients hypersensitive to codeine.

DOSAGE AND ADMINISTRATION

Adults: 2 tablets to be taken with water every four to six hours if necessary. Maximum 8 tablets in 24 hours. Do not use in children aged below 18 years.

Do not exceed the stated dose or take for more than three days without a doctor's advice.

If symptoms persist or worsen medical advice should be sought.

Should not be used with other paracetamol or codeine products.

Must not be used in children under 18 years of age.

OVERDOSAGE

If an overdose is taken or suspected, phone the Poisons Information Centre should be contacted immediately for advice (131 126), or the patient should go to the hospital straight away, even if they feel well, because of the risk of delayed, serious liver damage.

Effects of overdose due to codeine would be subsumed by the serious liver toxicity caused by paracetamol overdose.

Paracetamol

Paracetamol overdose may cause liver failure.

Treatment

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present.

Administration of N-acetylcysteine may be required.

Codeine

An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

Treatment

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 an hour of ingestion of more than 350 mg of codeine or a child more than 5 mg/kg of codeine.

Give naloxone if coma or respiratory depression is present. Observe for at least four hours after ingestion or eight hours for a sustained release formulation.

PRESENTATION AND STORAGE CONDITIONS

Capsule-shaped tablets (white, marked PAN 15): 12s, 24s and 40s (retail pack) and 6s (health professional sample pack).

Not all pack sizes may be marketed.

Store below 30 degrees Celsius. Keep out of reach of children.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue
ERMINGTON NSW 2115

POISON SCHEDULE OF THE MEDICINE

S3 - PHARMACIST ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13 May 2004

DATE OF THE MOST RECENT AMENDMENT

November 2015

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