New Zealand Data Sheet

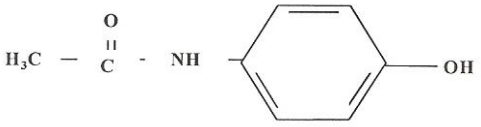
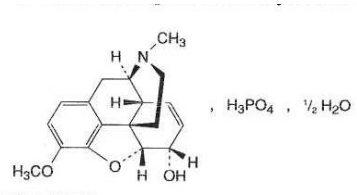
1. NAME OF MEDICINE

Panadeine® Tablets / Caplets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500mg, Codeine Phosphate 8mg

3. PHARMACEUTICAL FORM

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

Tablets: Flat, round white 1.27cm tablet with bevelled edges. Front face marking "PANADEINE" with a break bar on the back face

Caplets: white, uncoated capsule-shaped tablets, marked Panadeine with break-bar on the back face

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the temporary relief of pain and discomfort associated with

- Headache
- Migraine headache
- Tension headache
- Period pain
- Back pain
- Muscle pain
- Arthritis
- Toothache
- Neuralgia
- Cold & flu symptoms
- Dental procedures
- Sore throat

Reduces fever.

4.2 Dosage and Administration

18 years - Adults:

2 tablets/caplets – to be taken with water four to six hours if necessary. Maximum 8 tablets/caplets 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 doctors advice.

If symptoms persist or worsen medical advice must be sought.

Should not be used with other paracetamol or codeine-containing products.

Must not be used in children under 18 years.

4.3 Contraindications

- Previous history of hypersensitivity to paracetamol, codeine, opioid analgesics, or excipients.
- Active alcoholism
- Acute respiratory depression
- In mothers who are breastfeeding.
- Under the age of 18 years.
- 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.

4.4 Special Warnings and Precautions for Use

Adults: Not to be taken for more than three days unless on the advice of a doctor.

Panadeine should be administered with caution to patients with hepatic or renal dysfunction.

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 antidepressants and phenothiazine
Monoamine Oxidase Inhibitors (MAOIs)
Warfarin and other coumarins

Prolonged use of high doses of codeine may produce dependence.

Panadeine Rapid Soluble which contains 413mg of sodium per tablet, should be used with caution if restricted salt intake is indicated.

Panadeine Rapid Soluble tablets contain aspartame (E951), a source of phenylalanine. Patients with phenylketonuria should not take this medicine.

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

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.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Panadeine with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Section 4.5 Interactions with other medicines and other forms of interaction].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid

analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Panadeine is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Section 4.5 Interactions with other medicines and other forms of interaction].

Use in Children
Not recommended for children under 18 years of age.

4.5 Interactions with other medicines and other forms of interactions
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.

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

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

Opiate analgesics may interact with MAOIs and result in serotonin syndrome.

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

Benzodiazepines and other Central Nervous System (CNS) depressants: Concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Section 4.4 Warnings and Precautions]. Examples of medicines which interact are:

benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquillizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

4.6 Fertility, Pregnancy and Lactation

Use in 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 physician. This includes maternal use during labour 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.

Use in Lactation
Codeine-containing products must not be used while breastfeeding.

4.7 Effects on ability to drive and use machinery
Codeine may cause drowsiness or a decrease in alertness in some patients. Patients should be cautioned about operating vehicles or machinery, or engaging in activities which require them to be fully alert.

4.8 Undesirable 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.

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/labeled 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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥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	*Thrombocytopaenia*
Immune system disorders	*Anaphylaxis* *Cutaneous hypersensitivity reactions including, among others, skin rashes, angiodema, Stevens Johnson syndrome and toxic epidermal necrolysis*
Respiratory, thoracic and mediastinal disorders	*Bronchospasm, especially in patients sensitive to aspirin and otherNSAIDs.*
Hepatobiliary disorders	*Hepatic dysfunction*

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	*Drug dependency can occur after prolonged use of codeine at higher doses*
Gastrointestinal disorders	*Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy*
Nervous system disorders	*Dizziness, worsening of headache with prolonged use, drowsiness.*
Skin and subcutaneous skin disorders	*Pruritus, sweating*

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

4.9 Overdose

If an overdose is taken or suspected, 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 which can lead to liver transplant or death. Acute pancreatitis has been observed with hepatic dysfunction.

Treatment

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

Administration of N-acetylcysteine or methionine 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

5.2 Pharmacokinetic Properties

After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma levels occur 30 to 120 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets -
Starch-maize, talc-purified, stearic acid, povidone, starch-pregelatinised maize, potassium sorbate.

Caplets –
Starch-maize, talc-purified, stearic acid, povidone, starch-pregelatinised maize, potassium sorbate.

6.2 Incompatibilities
No known incompatibilities

6.3 Shelf life
Shelf life of the product is 24 months from the date of manufacture.

6.4 Special precautions for storage
Store below 30°C.
Keep out of reach of children.

6.5 Nature and contents of container
Blister packs of 12, 24, 40 tablet/caplets.

7. MEDICINE SCHEDULE
Restricted Medicine

8. SPONSOR
GlaxoSmithKline Consumer Healthcare
Level 11, Zurich House
21 Queen Street
Auckland 1010
New Zealand
FREECALL NZ: 0800 540 144

9. DATE OF FIRST APPROVAL
2 April 2009

10. DATE OF REVISION OF THE TEXT
4 May 2017

Summary table of changes

Section changes	**Summary of new changes**
All	Transferred to new data sheet template