

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calpol Six Plus 250mg/5ml Sugar/Colour Free Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CALPOL SIX PLUS SUGAR/COLOUR FREE SUSPENSION contains Paracetamol 250 mg per 5 ml.

Excipients with known effect:

Maltitol (E965) 2040mg per 5ml
Sorbitol (E420) 1400mg per 5ml
Sodium 1.8mg per 5ml
Propylene glycol (E1520) 20.92 mg per 5ml
Benzyl alcohol 0.05 mg per 5ml
Ethanol 0.0008mg per 5ml
Methyl parahydroxybenzoate (E218) 5.0mg per 5ml
Propyl parahydroxybenzoate (E216) 1.0mg per 5ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Suspension

An off-white oral suspension with an odour of strawberries.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Calpol products are indicated for the treatment of mild to moderate pain and as antipyretics.

Calpol is indicated for the symptomatic relief of headache, migraine, neuralgia, toothache and teething pains, sore throat, influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Children aged 6 years – 12 years:

Child's Age	How Much	How often (in 24 hours)
6 – 8 years	One 5 ml spoonful (large end)	4 times
8 – 10 years	One 5.0 ml spoonful (large end) and one 2.5ml spoonful (small end)	4 times
10 – 12 years	Two 5 ml spoonfuls (large end)	4 times
<ul style="list-style-type: none">Do not give more than 4 doses in any 24-hour periodLeave at least 4 hours between dosesDo not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacistDo not give to children under the age of 6 years.It is important to shake the bottle for at least 10 seconds before use.		

Children aged 12 – 16 years:

Two - three 5ml spoonfuls (large end) up to 4 times a day.

Adults and children over 16 years:

Two - four 5ml spoonfuls (large end) up to 4 times a day.

Children under 6 years:

Not recommended.

Renal impairment:

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician.

Recommended Dose for Adults with Renal Impairment:

Glomerular filtration rate	Dose
10-50 ml/min	500mg (10 ml) every 6 hours
<10ml/min	500mg (10 ml) every 8 hours

Hepatic impairment

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. For adults, the daily dose should not exceed 2g per day unless otherwise directed by a physician.

The Elderly:

Experience has indicated that normal adult dosage is usually appropriate. However, in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

For certain patient groups, a reduced maximum daily dose should be considered unless directed by a physician:

- Patients who are underweight (for adults, those under 50kg)
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

For adults the maximum daily dose should not exceed 60mg/kg/day (up to 2g per day).

Method of Administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindicated in children under 6 years.

4.4 Special warnings and precautions for use

Paracetamol should be administered with caution under the following circumstances (see section 4.2):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment ($GFR \leq 50 \text{ ml/min}$)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency

- Dehydration
- Chronic malnutrition
- Patients who are underweight (for adults, those under 50 kg)
- Elderly In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses. If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted. Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately. Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors. Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity. Contains 2.04g Maltitol and 1.4g Sorbitol per 5ml. Sorbitol and maltitol may cause gastrointestinal discomfort and have a mild laxative effect. Patients with hereditary problems of fructose intolerance (HFI) should not take/be given this medicine. Calorific value 2.3kcal/g maltitol. Methyl and propyl parahydroxybenzoates may cause allergic reactions (possibly delayed). This medicine contains less than 1 mmol sodium (23 mg) per 5ml, that is to say essentially 'sodium-free'. This medicine contains 20.92mg propylene glycol (E1520) in each 5ml dose, which is equivalent to 4.18mg/ml. This medicine contains 0.05mg benzyl alcohol in each tablet. High volumes should be used with caution and only if necessary, especially in subjects who are pregnant or breastfeeding, or subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). This medicine contains 0.00075mg of alcohol (ethanol) in each 5ml which is equivalent to 0.00015 mg/ml. The amount in 5 ml is equivalent to less than 1ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

The use of drugs which induce hepatic microsomal enzymes, such as anticonvulsants and oral contraceptives, may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentrations of the drug and a faster elimination rate.

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

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity.

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest possible dose, for the shortest possible time at the lowest possible frequency.

When given to the mother in labelled doses, paracetamol crosses the placenta into the foetal circulation as early as 30 minutes after ingestion and is effectively metabolised by foetal sulphate conjugation.

Breastfeeding

Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose). Maternal ingestion of paracetamol at the recommended dose is not considered to present a risk to the nursing infant.

4.7 Effects on ability to drive and use machines

CALPOL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with paracetamol are listed below by System Organ Class (SOC). The frequencies are defined according to the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

The ADRs identified are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

System Organ Class (SOC)	Frequency category	Adverse Drug Reaction Preferred Term
Blood and lymphatic system disorders	Not known	Agranulocytosis
	Not known	Haemolytic anaemia
	Not known	Thrombocytopenic purpura
Immune system disorders	Rare	Hypersensitivity
	Not known	Anaphylactic reaction
Hepatobiliary disorders	Not known	Hepatic function abnormal
	Not known	Hepatic necrosis
Skin and subcutaneous tissue disorders	Rare	Rash
	Not known	Fixed eruption
	Not known	Rash pruritic
	Not known	Urticaria
Renal and urinary disorders	Uncommon	Nephropathy toxic
	Not known	Renal papillary necrosis (after prolonged administration)
Investigations	Not known	Transaminases increased
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis

Liver damage has been reported after daily ingestion of excessive amounts of paracetamol. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of their disease improved after paracetamol withdrawal.

Low level transaminase elevations may occur in some patients taking labelled doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

Very rare cases of serious skin reactions have been reported.

High anion gap metabolic acidosis.

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4).

Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Please refer to local guidelines for the treatment of paracetamol overdose.

Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, hyperhidrosis, malaise, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults and adolescents who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amount
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

The following sequelae to acute hepatic failure may be observed following overdose with paracetamol, are considered expected and may be fatal.

Expected Sequelae to Acute Hepatic Failure Associated with Paracetamol Overdose**Infections and Infestations:**

Sepsis, Fungal infection, Bacterial infection

Blood and Lymphatic System Disorders:

Disseminated intravascular coagulation, Coagulopathy, Thrombocytopenia

Metabolism and Nutrition Disorders:

Hypoglycaemia, Hypophosphatemia, Metabolic Acidosis, Lactic Acidosis

Nervous System Disorders:

Coma (with massive paracetamol overdose or multiple drug overdose), Encephalopathy, Brain oedema

Cardiac Disorders:

Cardiomyopathy, Cardiac arrhythmias

Vascular Disorders:

Hypotension

Respiratory, Thoracic and Mediastinal Disorders:

Respiratory failure

Gastrointestinal Disorders:

Pancreatitis, Gastrointestinal haemorrhage

Renal and Urinary Disorders:

Acute renal failure with acute tubular necrosis

General Disorders and Administration Site Conditions:

Multi-organ failure

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

Management

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties****ATC Code: N02BE01 – other analgesics and antipyretics**

Paracetamol is a centrally acting, non-opiate, non-salicylate analgesic. Paracetamol is a clinically proven analgesic/antipyretic, and it is thought to produce analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Single-dose studies (12.5 mg/kg) of paracetamol in febrile children showed an onset of fever reduction within 15 to 30 minutes.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract. Peak plasma concentrations are reached 30-90 minutes post dose and the plasma half-life is in the range of 1 to 3 hours after therapeutic doses. Drug is widely distributed throughout most body fluids following therapeutic doses. 90-100% of the drug is recovered in the urine within 24 hours almost entirely following hepatic conjugation with glucuronic acid (about 60%), sulphuric acid (about 35%) or cysteine (about 3%). Small amounts of hydroxylated and deacetylated metabolites have also been detected. Children have less capacity for glucuronidation of the drug than do adults. In overdosage there is increased N-hydroxylation followed by glutathione conjugation. When the latter is exhausted, reaction with hepatic proteins is increased leading to necrosis.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltitol Liquid (E965)
Sorbitol Liquid (non-crystallising) (E420)
Glycerol
Dispersible Cellulose
Xanthan Gum
Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Acesulfame Potassium
Polysorbate 80
Sodium Saccharin
Flavour, Strawberry Cream 11407-33 (containing propylene glycol (E1520) and benzyl alcohol)
Flavour, Strawberry 500286E (containing propylene glycol (E1520) and ethanol)
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light. Keep the bottle tightly closed.

6.5 Nature and contents of container

Amber glass bottle closed with a two-piece plastic screw child resistant, tamper evident closure fitted with a polyethylene or polyvinylidene chloride (PVDC) laminate faced wad.

Or

Amber glass bottle closed with a three-piece screw child resistant, tamper evident closure fitted with a polyethylene or polyvinylidene chloride (PVDC) laminate faced wad.

Or

Amber glass bottle closed with a two-piece screw child resistant, tamper evident closure fitted with a polyethylene laminate faced wad.

Or

Amber glass bottle closed with a plastic screw closure or a metal Roll-on-pilfer-proof closure fitted with a polyethylene or polyvinylidene chloride (PVDC) faced wad.

A spoon with a 2.5ml and 5ml measure is supplied with all packs of this product.

Package sizes: 60ml, 70ml, 100ml, 140ml, 500ml or 1000ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Shake well before use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA23490/003/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 1994

Date of last renewal: 14th October 2009

10 DATE OF REVISION OF THE TEXT

February 2025