

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calpol 120 mg/ 5 ml Sugar Free Infant Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calpol Sugar Free Infant Oral Suspension contains 120 mg Paracetamol in each 5 ml.

Excipients with known effect (per 5ml):

Maltitol Liquid (E965) 2.0 ml
Sorbitol Solution (E420) 0.75 ml
Sodium 0.86mg
Benzyl alcohol 0.16mg
Propylene glycol (E1520) 14.32mg
Ethanol 0.0007mg
Ethyl Parahydroxybenzoate (E214) 2.0 mg
Methyl Parahydroxybenzoate (E218) 5.0 mg
Propyl Parahydroxybenzoate (E216) 1.0 mg
Carmoisine (E122) 0.075 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Suspension

A pink suspension with a strawberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CALPOL Sugar Free Infant Suspension is indicated for the treatment of pain (including teething pain), and as an antipyretic.

Calpol Sugar Free Infant Suspension is indicated for the relief of headache, migraine, neuralgia, toothache and teething pains, sore throat, rheumatic aches and pains, influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Posology

Infants aged 2-3 months:

Age : 2 – 3 months	Dose
1. Post-vaccination fever	2.5 ml If necessary, after 4 - 6 hours, give a second 2.5 ml dose
2. Other causes of Pain and Fever - if your baby weighs over 4 kg and was born after 37 weeks	
• Do not give to babies less than 2 months of age. • Do not give more than 2 doses unless your doctor or nurse has advised otherwise. • Leave at least 4 hours between doses. • If further doses are needed, talk to your doctor or pharmacist. • It is important to shake the bottle for at least 10 seconds before use.	

Children aged 3 months – 6 years:

Child's Age	How Much	How often (in 24 hours)
3 – 6 months	2.5 ml	4 times
6 – 24 months	5 ml	4 times
2 – 4 years	7.5ml (5 ml + 2.5 ml)	4 times
4 – 6 years	10ml (5 ml + 5 ml)	4 times
- Do not give more than 4 doses in any 24 hour period - Leave at least 4 hours between doses - Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist		

The Elderly:

In the elderly, the rate and extent of paracetamol absorption is normal but plasma half-life is longer and paracetamol clearance is lower than in young adults.

Hepatic / renal dysfunction

Caution should be exercised when administering the product to patients with severe hepatic or renal impairment.

4.3 Contraindications

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

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. This product contains the following excipients which have recognised effects:

- Carmoisine (E122) which may cause allergic reactions.
- Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Ethyl parahydroxybenzoate (E214) which 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 14.32mg propylene glycol (E1520) in each 5ml dose, which is equivalent to 2.86mg/ml. This medicine contains 0.16mg 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 0.00071mg of alcohol (ethanol) in each 5ml which is equivalent to 0.000142 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. Due to the sorbitol (E420) and maltitol (E965) content of this product, patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol and maltitol may cause gastrointestinal discomfort and have a mild laxative effect. Calorific value 2.3kcal/g maltitol.

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 that 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 $\geq 1/100$ and $< 1/10$

Uncommon $\geq 1/1,000$ and $< 1/100$

Rare $\geq 1/10,000$ and $< 1/1,000$

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 the 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

Symptoms and signs

Hepatic necrosis is a dose-related complication of paracetamol overdose. In adults and adolescents (> 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (<12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise.

If a paracetamol extended release product is involved, it may be appropriate to obtain an additional plasma paracetamol level 4-6 hours following the initial paracetamol level.

Serious toxicity or fatalities have been extremely infrequent following an acute paracetamol overdose in young children, possibly because of differences in the way they metabolize paracetamol.

The following are clinical events associated with paracetamol overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Adverse Drug Reactions Identified with Overdose of Paracetamol

Metabolism and Nutrition Disorders:

Anorexia

Gastrointestinal Disorders:

Vomiting, Nausea, Abdominal discomfort

Hepatobiliary Disorders:

Hepatic necrosis, Acute (fulminant) hepatic failure, Jaundice, Hepatomegaly, Liver tenderness

General Disorders and Administration Site Conditions:

Pallor, Hyperhidrosis, Malaise

Investigations:

Blood bilirubin increased, Hepatic enzymes increased, International normalised ratio increased, Prothrombin time prolonged, Blood phosphate increased, Blood lactate increased

The following clinical events are sequelae to acute hepatic failure and may be fatal. If these events occur in the setting of acute hepatic failure associated with paracetamol overdose (adults and adolescents: ≥ 12 years of age: >7.5 g within 8 hours; children <12 years of age: >150 mg/kg within 8 hours), they are considered expected.

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

Treatment

To protect the patient against delayed hepatotoxicity, paracetamol overdosage should be treated promptly by gastric lavage followed by intravenous N-acetylcysteine or oral methionine. Additional therapy (further methionine or intravenous cysteamine or intravenous N-acetylcysteine) is normally considered in the light of blood paracetamol content and the time elapsed since ingestion. Fulminant hepatic failure which may follow paracetamol overdosage requires specialised management.

In paracetamol overdosage with liver cell damage, paracetamol half-life is often prolonged from around 2 hours in normal adults to 4 hours or longer.

However liver cell damage has been found in patients with a paracetamol half life less than 4 hours. Diminution of $^{14}\text{CO}_2$ excretion after ^{14}C -aminopyrine has been reported to correlate better with liver cell damage in paracetamol overdosage than do either plasma paracetamol concentration or half-life, or conventional liver function test measurements.

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 centre. 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 gastrointestinal 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 solution (70% non-crystallising) (E420)

Glycerol

Dispersible cellulose
Xanthan gum
Ethyl Parahydroxybenzoate (E214)
Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Polysorbate 80
Strawberry flavour 50086E (containing propylene glycol (E1520), benzyl alcohol and ethanol)
Carmoisine (E122)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep in original container.

6.5 Nature and contents of container

A. 5ml sachet composed of a complex made of paper/PE/aluminium/Surlyn. Pack sizes: 10 x 5 ml, 12 x 5 ml and 20 x 5 ml. A spoon with a 5 ml and 2.5 ml measure is supplied with this pack.

B. 60ml, 70ml, 100ml and 140ml amber glass bottle with a two-piece plastic child resistant, tamper evident closure fitted with a polyethylene or polyvinylidene chloride (PVDC) laminate faced wad. A spoon with a 5 ml and 2.5 ml measure is supplied with all packs of this product.

C. 60ml, 70ml, 100ml and 140ml amber glass bottle with a three-piece plastic child resistant, tamper evident closure fitted with a polyethylene or polyvinylidene chloride (PVDC) laminate faced wad. A spoon with a 5 ml and 2.5 ml measure is supplied with all packs of this product.

D. 60ml, 70ml, 100ml and 140ml Amber glass bottle with a two-piece white plastic child-resistant external cap (in polypropylene), fitted with an inner plastic cap, including a tamper evident ring, in high density polyethylene (HDPE). The cap contains a plug made of Low Density Polyethylene (LDPE). A measuring syringe is provided in the secondary packaging. The syringe is made of polypropylene for the barrel and of violet-coloured high density polyethylene (HDPE) for the plunger.

E. 60ml, 70ml, 100ml and 140ml Amber glass bottle with a two-piece white plastic child-resistant external cap (in polypropylene), fitted with an inner plastic cap, including a tamper evident ring, in high density polyethylene (HDPE). A HDPE disk platine and a Press-In-Bottle Adapter (PIBA, commonly named plug), made of Low-Density Polyethylene (LDPE). A measuring syringe is provided in the secondary packaging. The syringe is made of polypropylene for the barrel and of violet-coloured high density polyethylene (HDPE) for the plunger.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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