SUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of the Medicinal Product

Calpol 120mg/5ml Infant Oral Suspension

2. Qualitative and Quantitative Composition

Calpol Infant Oral Suspension contains -

Paracetamol 120 mg per 5 ml.

Excipients with known effect (per 5ml):

Sucrose	2202.48mg
Sorbitol Liquid (E420)	451.5mg
Methyl parahydroxybenzoate (E218)	5.0mg
Propyl parahydroxybenzoate (E216)	1.0mg
Ethyl parahydroxybenzoate (E214)	2.0mg
Carmoisine (E122)	0.075mg

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Oral Suspension.
A viscous pink coloured suspension with a strawberry odour and taste.

4. Clinical Particulars

4.1 Therapeutic Indications

Calpol Infant Oral Suspension is indicated for the treatment of pain (including teething pain), and as an antipyretic.

4.2 Posology and Method of Administration

Infants aged 2-3 months:

<table>
<tr><th>Age: 2 – 3 months</th><th>Dose</th></tr>
<tr><td>1. Post-vaccination fever</td><td rowspan="2">2.5 ml

If necessary, after 4-6 hours, give a second 2.5 ml dose</td></tr>
<tr><td>2. Other causes of Pain and Fever - if your baby weighs over 4 kg and was born after 37 weeks</td></tr>
<tr><td colspan="2">• Do not give to babies less than 2 months of age.</td></tr>
</table>

- 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

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. Patients should be advised to contact their healthcare professional before use.

Hepatic impairment:

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. Patients should be advised to contact their healthcare professional before use.

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:

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

These patients should be advised to contact their healthcare professional before use.

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.

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≤50ml/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 cases medical assistance should be sought immediately.

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:

- Sucrose and sorbitol. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Contains 2.2 g of sucrose per 5 ml. This should be taken into account in patients with diabetes mellitus.
- Sorbitol may cause gastrointestinal discomfort and have a mild laxative effect.
- Carmoisine (E122) which may cause allergic reactions.
- Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Ethyl parahydroxybenzoate (E214) which may cause allergic reactions (possibly delayed).

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.

4.6 Fertility, pregnancy & lactation

There are no adequate and well-controlled clinical studies in pregnant or breastfeeding women.

Pregnancy

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.

While paracetamol has been used to treat pregnant women for many years, as for all medicines, paracetamol should only be used in pregnancy when necessary, and at the lowest possible dose, for the shortest duration of time. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in recommended dosage, but patients should follow the advice of their doctor regarding its use.

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 ≥1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare≥ 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	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

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.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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 patients 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 amounts

- 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 Pharmacodynamics

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 Pharmacokinetics

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 Pre-clinical safety Data

Mutagenicity

There are no studies relating to the mutagenic potential of Calpol Sugar Free Infant Suspension.

In vivo mutagencicity tests of paracetamol in mammals are limited and show conflicting results. Therefore, there is insufficient information to determine whether paracetamol poses a mutagenic risk to man.

Paracetamol has been found to be non-mutagenic in bacterial mutagenicity assays, although a clear clastogenic effect has been observed in mammalian cells *in vitro* following exposure to paracetamol (3 and 10 mM for 2 hr).

Carcinogenicity

There are no studies relating to the carcinogenic potential of Calpol Sugar Free Infant Suspension.

There is inadequate evidence to determine the carcinogenic potential of paracetamol in humans. A positive association between the use of paracetamol and cancer of the ureter (but not of other sites in the urinary tract) was observed in a case-control study in which approximate lifetime consumption of paracetamol (whether acute or chronic) was estimated. However, other similar studies have failed to demonstrate a statistically significant association between paracetamol and cancer of the urinary tract, or paracetamol and renal cell carcinoma.

There is limited evidence for the carcinogenicity of paracetamol in experimental animals. Liver cell tumours can be detected in mice and liver and bladder carcinomas can be detected in rats following chronic feeding of 500 mg/kg/day paracetamol.

Teratogenicity

There is no information relating to the teratogenic potential of Calpol Sugar Free Infant Suspension. In humans, paracetamol crosses the placenta and attains concentrations in the foetal circulation similar to those in the maternal circulation. Intermittent maternal ingestion of therapeutic doses of paracetamol is not associated with teratogenic effects in humans.

Paracetamol has been found to be fetotoxic to cultured rat embryo.

Fertility

There is no information relating to the effects of Calpol Sugar Free Infant Suspension. A significant decrease in testicular weight was observed when male Sprague-Dawley rats were given daily high doses of paracetamol (500 mg/kg body weight/day) orally for 70 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sorbitol Liquid (non-crystallising) (E420)
Glycerol
Xanthan gum
Dispersible Cellulose
Polysorbate 80
Acesulfame Potassium
Strawberry flavour, 500018E
Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Ethyl Parahydroxybenzoate (E214)
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. Store in the original container.

6.5 Nature and contents of container

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

B. 60ml, 70ml, 100ml and 140ml amber glass bottle with a three-piece plastic child resistant, tamper evident closure fitted with a polyethylene or polvinylidine 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 two-piece white plastic child-resistant external cap, fitted with an inner plastic cap, including a tamper evident ring, in high density polyethylene. 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.

Not all pack sizes may be marketed

6.6 Instructions for use/handling

No special requirements

7 Name and address of the holder of the marketing authorisation

Johnson & Johnson (Ireland) Limited
Airton Road
Tallaght
Dublin 24
Ireland

8 Marketing authorisation number

PA 330/17/1

9 Date of first authorisation/renewal of authorisation

Date of first authorisation: 1st April 1998
Date of last renewal: 1st April 2008

10 Date of revision

December 2018