Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calpol Six Plus 250mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains -
Paracetamol 250 mg.

Excipients with known effect:
Sucrose 2.1g/5ml, Sorbitol 1.89g/5ml, sodium 1.3mg/5ml, propylene glycol (E1520) 9.72mg /5ml, ethanol 0.0749mg /5ml, methyl parahydroxybenzoate (E218) 4mg/5ml and Sunset Yellow (E110) 0.25mg/5ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension
An orange coloured and flavoured viscous oral suspension.

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

- 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
- Do 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.

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)
- ElderlyIn 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. 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 sucrose and sorbitol. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Sorbitol may cause gastrointestinal discomfort and have a mild laxative effect. Contains sunset yellow (E110) which may cause allergic reactions. Contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed). This medicine contains less than 1 mmol sodium (23 mg) per 5ml, that is to sayessentially 'sodium-free'. This medicine contains 9.72mg propylene glycol (E1520) in each 5ml dose, which is equivalent to 1.94mg/ml. This medicine contains 0.0749mg of alcohol (ethanol) in each 5ml which is equivalent to 0.01498 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 overdosage 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. 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	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 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 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

Absorption
Absorption of paracetamol occurs mainly by passive transfer from the small intestine. Gastric emptying is the rate-limiting step in the absorption of orally-administered paracetamol. Any drug, disease or other condition which alters the rate of gastric emptying will therefore influence the rate of paracetamol absorption.Peak plasma paracetamol concentration usually occurs between 30 and 90 minutes after oral ingestion, depending on the formulation. Mean maximum plasma concentrations of paracetamol of 12.84 ug/ml were determined following the administration of CALPOL Six Plus suspension (containing 1g paracetamol) to adults.

Paracetamol is incompletely available to the systemic circulation after oral administration since a variable proportion is lost through first-pass metabolism. Oral bioavailability in adults appears to depend on the amount of paracetamol administered, increasing from 63% of the administered dose after 500mg to nearly 90% of the dose after 1 or 2 g (in tablet form).

Distribution
Paracetamol is distributed uniformly throughout most body fluids with an estimated volume of distribution of 0.95 l/kg.

Following therapeutic doses, paracetamol is not appreciably bound to plasma proteins.

Metabolism and elimination
The plasma half-life of paracetamol after therapeutic doses is in the range 1.5-2.5 hours. Paracetamol is metabolised by the liver and several metabolites of paracetamol have been identified in man. The two major metabolites excreted in the urine are the glucuronide and sulphate conjugates. About 10 % of administered paracetamol is converted, via a minor pathway, by a cytochrome P-450 mixed function oxidase system to a reactive metabolite, acetamidoquinone. This metabolite is rapidly conjugated with reduced glutathione and excreted as cysteine and mercapturic acid conjugates. When large amounts of paracetamol are taken, hepatic glutathione may become depleted causing excessive accumulation within the hepatocyte of acetamidoquinone, which binds covalently to vital hepatocellular macromolecules. In overdose, this can lead to hepatic necrosis. Total body clearance of paracetamol following a single dose (1000 mg i.v) is approximately 5 ml/min/kg.

Renal excretion of paracetamol involves glomerular filtration and passive reabsorption, and the sulphate and glucuronide conjugates are subject to active renal tubular secretion. Renal clearance of paracetamol depends on urine flow rate, but not pH.

Less than 4 % of the administered drug is excreted as unchanged paracetamol. In healthy subjects, approximately 85-95% of a therapeutic dose is excreted in the urine within 24 hours.

Pharmacokinetics in Renal Impairment
The mean plasma half life of paracetamol is similar in normal and renally impaired subjects between 2-8hrs, but from 8-24hrs paracetamol is eliminated less rapidly. Marked accumulation of the glucuronide and sulphate conjugates occurs in chronic renal failure. There may be some extra renal elimination of retained paracetamol conjugates in patients with chronic renal failure, with limited regeneration of the parent compound. An increase in the interval between doses of paracetamol has been recommended for adults with chronic renal failure.Haemodialysis may result in reduced plasma levels of paracetamol.Supplementary doses of paracetamol may be necessary in order to maintain therapeutic blood levels.

Pharmacokinetics in Hepatic Impairment
The mean plasma paracetamol half-life is similar in normal subjects and those with mild liver disease, but is significantly prolonged (approximately 75%) in patients with severe liver disease.

However, the clinical significance of the increase in half-life is unclear, since there is no evidence of drug accumulation or hepatotoxicity in patients with liver disease, and glutathione conjugation is not impaired.

The administration of 4g paracetamol daily for 13 days to 20 subjects with chronic stable liver disease, resulted in no deterioration of liver function, and in mild liver disease, there is no evidence that paracetamol is harmful when taken at recommended doses. However, in severe liver disease, the plasma paracetamol half-life is significantly prolonged.

Pharmacokinetics in the Elderly
Differences in pharmacokinetic parameters observed between fit young and fit elderly subjects are not thought to be of clinical significance. However, there is some evidence to suggest that serum paracetamol half-life is markedly increased (by approximately 84%), and clearance of paracetamol is decreased (by approximately 47%) in frail, immobile, elderly subjects when compared to fit young subjects.

Pharmacokinetics in children
Studies have shown that in neonates 0-2 days old and children 3-10 years old, paracetamol sulphate is the major metabolite of paracetamol, whereas data in adults and children of 12 years of age and over demonstrate that the major metabolite is the glucuronide conjugate . However, there are no significant age-related differences in the overall elimination rate of paracetamol or in the total amount of drug recovered in the urine.

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

CALPOL Six Plus Suspension contains the following excipients:

Sucrose Ph. Eur.
Sorbitol liquid, (non-crystallising) Ph. Eur. (E420)
Glycerol Ph. Eur. (E422)
Dispersible cellulose BP
Polysorbate 80 Ph. Eur.
Flavour (white sugar DA 13780) (containing propylene glycol (E1520))
Flavour (orange 510652E) (containing ethanol)
Methyl parahydroxybenzoate Ph. Eur. (E218)
F, D and C yellow No 6 soluble/Sunset Yellow FCF (E110)
Purified water Ph. Eur.

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 to protect from light.

6.5 Nature and contents of container

5ml Paper/aluminium foil/surlyn sachets.

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

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

Pack sizes: 60ml and 70ml.

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

JNTL Consumer Health I (Ireland) Limited
Office 5, 6 And 7
Block 5
High Street
Tallaght
Dublin 24
D24 YK8N
Ireland

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