Part II

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

Each 5ml contains 120mg of paracetamol.

Excipients:

Maltitol
Sorbitol
Carmoisine
Ethyl hydroxybenzoate
Propyl hydroxybenzoate
Methyl hydroxybenzoate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

Product imported from the UK:
A pink suspension with a strawberry colour

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

Children aged 6 years to 12 years:

Oral. 10 to 20 ml (240 mg to 480 mg paracetamol). Repeat every 4 hours, if necessary, up to a maximum of 4 doses per 24 hours.

Children aged 1 to under 6 years:

Oral. 5 to 10ml (120 mg to 240 mg paracetamol). Repeat every 4 hours, if necessary, up to a maximum of 4 doses per 24 hours.

Infants 3 months to under 1 year:

Oral. 2.5 to 5 ml (60 mg to 120 mg paracetamol). Repeat every 4 hours, if necessary, up to a maximum of 4 doses per 24 hours.

Infants 2-3 months (>3kg body weight)

Oral 2.5ml (60mg paracetamol) Repeat every 4 hours, if necessary, up to a maximum of 4 doses per 24 hours. Do not use for more than 2 days without medical supervision.

Under 2 months

Consult your doctor.

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

CALPOL Sugar Free Infant Suspension is contra-indicated in patients with known hypersensitivity to paracetamol, or any of the other components.

4.4 Special warnings and precautions for use

CALPOL Sugar Free Infant Suspension should be used with caution in moderate to severe renal impairment or severe hepatic impairment.

The label contains the following statements:
Store below 25°C. Protect from light.
Contains paracetamol.
Do not exceed the stated dose.
Keep out of reach of children.
Do not take more than 4 doses in 24 hours.
Dose 4 times a day.
Do not repeat doses more frequently than 4 hourly.
Do not give for more than 3 days without consulting a doctor.

In the case of infants less than 3 months, do not give for more than 2 days without consulting a doctor.
If symptoms persist consult your doctor.
If you child is taking any other medicine, consult your doctor or pharmacist before taking this product.

Immediate medical advice should be sought in the event of an overdose, even if you feel well. (label)
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of irreversible liver damage. (leaflet)
Do not take with any other paracetamol containing products.

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 paracetamol, resulting in reduced plasma concentrations of the 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 Pregnancy and lactation

The safe use of CALPOL Sugar Free Infant Suspension during pregnancy has not been established. There is epidemiological evidence of the safety of paracetamol in human pregnancy.

A pharmacokinetic study in 12 nursing mothers revealed that less than 1% of the dose ingested by a nursing mother appears in human breast milk, therefore maternal ingestion of therapeutic doses does not present a risk to the infant.

4.7 Effects on ability to drive and use machines

No special comment – unlikely to produce an effect.

4.8 Undesirable effects

Paracetamol has been widely used and, when taken at the usual recommended dosage, side effects are mild and infrequent and reports of adverse reactions are rare. Skin rash and other allergic reactions occur rarely.

Most reports of adverse reactions to paracetamol relate to overdosage with the drug.
Isolated cases of thrombocytic purpura, haemolytic anaemia and agranulocytosis have been reported.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods.

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.

Nephrotoxic effects following therapeutic doses of paracetamol are uncommon. Papillary necrosis has been reported after prolonged administration.

4.9 Overdose

Symptoms and signs

Pallor, anorexia, nausea and vomiting are frequent early symptoms of paracetamol overdosage, although in many cases there are no symptoms for many hours.

Hepatic necrosis is a dose-related complication of paracetamol overdose. Hepatic enzymes may become elevated and prothrombin time prolonged within 12 to 48 hours but clinical symptoms may not be apparent for 1 to 6 days after ingestion. Toxicity is likely in subjects who have taken single doses of 10 g.

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 $^{14}CO_2$ 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. Renal failure due to acute tubular necrosis may follow paracetamol-induced fulminant hepatic failure. The incidence of this is, however, no more frequent in these patients than in others with fulminant hepatic failure from other causes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol has analgesic and antipyretic effects similar to those of aspirin and is useful in the treatment of mild to moderate pain. It has weak anti-inflammatory effects.

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

Mutagenicity

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

In vivo mutagenicity 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 are 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

Maltitol liquid
Sorbitol (E420)
Glycerol
Dispersible Cellulose
Xanthan gum
Ethyl hydroxybenzoate (E214)
Propyl hydroxybenzoate (E218)
Methyl hydroxybenzoate (E216)
Polysorbate 80
Strawberry flavour
Carmoisine (E122)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date for this product shall be the date on the container and outer package of the product in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C
Store the bottle in the outer carton.

6.5 Nature and contents of container

Amber glass bottle, with child resistant closure, containing 100ml.
The bottle is packed in an outer cardboard carton.
A spoon with a 5ml and 2.5ml measure is supplied with all packs.

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 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 Parallel Product Authorisation Number

PA 0465/172/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28 April 2006

10 DATE OF REVISION OF THE TEXT

October 2008