Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calpol Sugar/Colour Free Infant Suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calpol Sugar/Colour Free Infant Suspension contains –

Paracetamol Ph. Eur. 120 mg per 5 ml.

3 PHARMACEUTICAL FORM

Oral Suspension.
An off-white suspension with an odour of strawberry.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of pain and fever associated with such conditions as common cold, influenza, headaches, teething.

4.2 Posology and method of administration

Aged over 6 years: The usual dosage is up to 20 ml (480 mg) four times daily

Aged 1 to 6 years: The usual dosage is 5 to 10 ml (120-240 mg) four times daily

Aged 3 months to 12 months: The usual dosage is 2.5 to 5 ml (60-120 mg) four times daily

Under 3 months: A 2.5 ml dose is suitable for babies who develop a fever following vaccination at 2 months. In other cases, use only under medical supervision.

4.3 Contraindications

Use in patients with a known hypersensitivity to paracetamol.

4.4 Special warnings and precautions for use

Calpol should be used with caution in patients with severe hepatic or renal dysfunction.

Special Labelling Requirements

Prolonged use except under medical supervision could be harmful.

Consult the doctor if there is no improvement within 24 hours.

Do not exceed the stated dose.

This product should only be used when clearly necessary.

Do not take with other products containing paracetamol.

Store below 25^{o}C.

Protect from light.

4.5 Interaction with other medicinal products and other forms of interaction

Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

Alcohol 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.

Chronic ingestion of anticonvulsants or oral steroid contraceptives induce liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism or clearance.

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

Data are not available on the use of Calpol during pregnancy. There is epidemiological evidence of 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 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

None known.

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 rashes and other allergic reactions occur rarely.

Most reports of adverse reactions to paracetamol relate to overdosage with the drug.

Isolated cases of thrombocytopenic purpura, haemolytic anaemia and agranulocytosis have been recorded.

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 their disease improved after paracetamol withdrawal.

Nephrotoxicity following therapeutic doses of paracetamol is uncommon, but papillary necrosis has been reported after prolonged administration.

4.9 Overdose

Pallor, anorexia, nausea and vomiting are frequent early symptoms of paracetamol overdosage. Hepatic necrosis is a dose-related complication of paracetamol over-dosage. Hepatic enzymes may become elevated and prothrombin time prolonged within 12-48 hours but clinical symptoms may not be apparent until 1 to 6 days after ingestion. Toxicity is likely in adults who have taken more than 10g.

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 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 in $^{14}CO_2$ excretion after oral ^{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. Concomitatnt renal failure due to acute tubular necrosis may accompany paracetamol-induced fulminate hepatic failure. The incidence of this is however, no more frequent in these patients than in others with fulminant hepatic failures 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 only weak anti-inflammatory effects.

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

Mutagenicity

There are no studies relating to the mutagenic potential of Calpol Sugar/Colour Free 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 10mM for 2h).

Carcinogenicity

There are no studies relating to the carcinogenic potential of Calpol Sugar/Colour 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 rats following chronic feeding of 500mg/kg/day paracetamol.

Teratogenicity

There is no information relating to the teratogenic potential of Calpol Sugar/Colour Free Infant Suspension. In humans, paracetamol crosses the placenta and attains concentration 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 foetotoxic to cultured rat embryo.

Fertility

There is no information relating to the effects of Calpol Sugar/Colour Free Infant Suspension on fertility. 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

Hydrogenated glucose syrup
Sorbitol solution (70%) (non-crystallising)
Glycerol
Dispersible cellulose
Xanthan gum
Flavour, strawberry
Methyl hydroxybenzoate
Purified water
Propyl hydroxybenzoate

6.2 Incompatibilities

None known.

6.3 Shelf Life

36 months unopened.

6.4 Special precautions for storage

Store below 25°C.
Protect from light.

6.5 Nature and contents of container

Amber glass bottles with a nominal capacity of 70, 100, 140 and 200 ml closed with a two-piece plastic child resistant, tamper evident closure fitted with a polyethylene/polyvinylidene chloride (PVDC).polyethylene laminate faced wad.

or

Amber glass bottles with a nominal capacity of 70, 100, 140 and 200 ml closed with a three-piece plastic child resistant, tamper evident closure fitted with a polyethylene/polyvinylidene chloride (PVDC)/Polyethylene laminate faced wad.

and

Amber glass bottles with a nominal capacity of 500 and 1000 ml with plastic screw caps with polyvinylidene chloride (PVDC) wads.

and

5 ml Paper/aluminium foil/polyethylene laminate sachets.

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

None acceptable.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd.,
Airton Road,
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 0823/010/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 1996

Date of last renewal: 16 February 2001

10 DATE OF REVISION OF THE TEXT

January 2005