2.16 Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT
PINNACLE PARACETAMOL INJECTION (Paracetamol Injection 300mg/2ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2ml contains:
Paracetamol BP.....300mg

3. PHARMACEUTICAL FORM
Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:
Paracetamol injection is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever when intravenous administration is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

4.2 Posology and method of administration:
Tablet: Orally, 0.5 to 1 g every 4 to 6 hours up to a maximum of 4g daily.

For Children:
Must be given every 4 to 6 hours when necessary up to max. of 4 doses in 24 hours.

3months to 1 year: 60 to 120mg
1 to 5 years: 120mg to 250mg
6 to 12 years: 250mg to 500mg

For Neonates:
(28 to 32 week) postmenstrual age:
20mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a max. of 30mg/kg daily. Over 32 weeks postmenstrual age: 20mg/kg as a single dose then 10 to 15mg/kg every 6 to 8 hours if necessary up to max. of 60mg/kg daily.
1 to 3 months of age: 30 to 60mg every 8 hours if necessary.

Children with more severe symptoms: children aged 1 to 3 months may be given 20 mg/kg as a single dose followed by 15 to 20 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily; older children may also be given 20 mg/kg every 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer if necessary followed by 15 mg/kg every 6 hours.

For post-immunisation pyrexia, a dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after six hours; if the pyrexia persists after that dose, medical advice should be sought.

Paracetamol may also be given as suppositories in an adult rectal dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Rectal doses in younger children:
neonates 28 to 32 weeks postmenstrual age, 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily

neonates over 32 weeks postmenstrual age, 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily

1 to 3 months of age, 30 to 60 mg every 8 hours if necessary to a maximum of 60 mg/kg daily

3 to 12 months of age, 60 to 125 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours

5 to 12 years of age, 250 to 500 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours

for severe symptoms, children aged 1 to 3 months may be given 30 mg/kg as a single dose followed by 20 mg/kg every 8 hours to a maximum of 60 mg/kg daily; older children may be given 40 mg/kg as a single dose followed by 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer, if necessary, before reducing to 15 mg/kg every 6 hours. Again, the usual adult maximum would apply in heavier children.

Paracetamol by **intravenous** infusion to adults and children over 10 kg in weight. Dosage may be calculated by weight as follows:
patients weighing over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less) between 10 and 33 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 2 g daily (whichever is less).

4.3 Contraindications:
Paracetamol injection is contraindicated:
- in patients with hypersensitivity to paracetamol or propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients
- in patients with severe hepatocellular insufficiency

4.4 Special warnings and precautions for use:
It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration is possible.

In order to avoid the risk of overdose, check that other medicines administered do not contain paracetamol or propacetamol.

Doses higher than those recommended entail the risk of very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of drug administration with a

peak seen usually after 4 - 6 days. Treatment with antidote must be given as soon as possible (see Section 4.9).

Precautions for use

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency
- severe renal insufficiency (creatinine clearance ≤ 30 ml/min (see Sections 4.2 and 5.2)
- chronic alcoholism
- chronic malnutrition (low reserves of hepatic glutathione)
- dehydration

4.5 Interaction with other medicinal products and other forms of interaction:

Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination half-life of paracetamol.

Particular care must be exercised when enzymatic inductors are administered concomitantly (see Section 4.9).

Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

4.6 Fertility, pregnancy and lactation:

Pregnancy

Clinical experience of the intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects in pregnancy or on the health of the foetus / newborn infant.

Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.

No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not shown any malformation or foetotoxic effects.

Nevertheless, Paracetamol Injection should only be used during pregnancy after a careful benefit/risk assessment. In this case, the recommended dose and duration of treatment must be strictly observed.

Lactation

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effect on nursing infants have been reported. Consequently, Paracetamol Injection may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines:
Not Applicable.

4.8 Undesirable effects:
As with all medicines containing paracetamol, adverse drug reactions are rare (> 1/10 000, < 1/1000) or very rare (< 1/10 000). These are described below.

MedDRA- system organ class database	Rare > 1/10 000, < 1/1000	Very rare < 1/10 000
General disorders and administration site conditions	Malaise	
Immune system disorders		Hypersensitivity reaction
Vascular disorders	Hypotension	
Hepatobiliary disorders	Increased levels of hepatic transaminases	
Blood and lymphatic system disorders		Thrombocytopenia Leucopenia Neutropenia

Pain or burning sensation at the injection site have been reported, which may result from the rate at which the infusion is administered and which is not necessarily resolved by decreasing infusion rate.

Erythema, flushing, pruritus and tachycardia have been reported in some cases.

Very rare cases of serious skin reactions have been reported. Hypersensitivity reactions ranging from a simple skin rash or urticaria to anaphylactic shock, requiring discontinuation of treatment have been reported in very rare cases.

4.9 Overdose:
There is a risk of liver damage (including fulminant hepatitis, liver insufficiency, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdose may be fatal in these cases.

Symptoms generally appear within 24 hours and include: nausea, vomiting, anorexia, pallor and abdominal pain.

Overdose, 7.5 g or more of paracetamol in a single administration in adults and 140 mg/kg of body weight in a single administration in children causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis, encephalopathy which may lead to a coma and death.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration.
Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

Emergency measures
- Immediate hospitalisation
- Before beginning treatment, take a blood sample for plasma paracetamol assay as soon as possible after the overdose.
- Treatment for an overdose includes the oral or intravenous administration of the antidote Nacetylcysteine (NAC), if possible before the 10th hour. However NAC may give some degree of protection even after 10 hours, and prolonged treatment should be given in this case.
- Symptomatic treatment
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours
- In most cases hepatic transaminases return to normal in one to two weeks with full restitution of the liver function. In very severe cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic class: OTHER ANALGESICS AND ANTIPYRETICS, Code ATC: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established and may involve central and peripheral actions.

Paracetamol Injection provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

Paracetamol Injection reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacokinetic properties:
Absorption
Paracetamol pharmokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g of Paracetamol Injection is similar to that observed following infusion of 1 g and 2 g propacetamol (containing 500 mg and 1 g of paracetamol respectively).

The maximum plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of Paracetamol Injection is about 15 µg/ml and 30 µg/ml respectively.

Distribution

- The volume of distribution of paracetamol is approximately 1 l/kg
- Paracetamol is not extensively bound to plasma proteins

Metabolism

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive poisoning, the quantity of this toxic metabolite is increased.

Elimination

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted within 24 hours, mainly as glycuronide (60 to 80%) and sulphate (20 to 30%) conjugates.

Less than 5% is eliminated unchanged.

Plasma half-life is 2.7 hours and total body clearance approximately 18 l/h.

FULL-TERM NEWBORNS, INFANTS AND CHILDREN

The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 h) than in adults. In newborn infants, the plasma half-life is longer than in infants i.e. around 3.5 hours. Newborn infants, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table. Age related pharmacokinetic values (standardised clearance: *CLstd/Foral (l.h-1 70kg-1) are described below:

Age	Weight (kg)	CLstd/Foral (l.h-1 70kg-1)
40 weeks PCA	3.3	5.9
3 months PNA	6	8.8
6 months PNA	7.5	11.1
1 year PNA	10	13.6
2 year PNA	12	15.6
5 year PNA	20	16.3
8 year PNA	25	16.3

*CLstd is the population estimate for CL

Special precautions

Renal insufficiency

In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects.

Therefore when giving paracetamol to patients with severe renal impairment (creatinine clearance £ 30 mL/min), the minimum interval between each administration should be increased to at least 6 hours (see section 4.2).

Elderly subjects
The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

5.3 Preclinical safety data
Preclinical data reveal no other special hazard for beyond the information included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polyethylene glycol 400
Benzyl alcohol
Lidocaine
Anhydrous sodium sulphite
Disodium Edetate (EDTA-2Na)
Water for injection

6.2 Incompatibilities
In the absence of incompatibility studies, the products must not be mixed with other medicinal products.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C in a dry place. Do not refrigerate or freeze.
Keep out of reach of children.

6.5 Nature and contents of container
Paracetamol Injection is supplied in packs of 10 x 2ml amber coloured glass ampoules (Type I) with blue spot on neck along with a pack insert.

6.6 Special precautions for disposal and other handling
None.

7. MARKETING AUTHORISATION HOLDER
Eliona Pharmaceutical Company Limited.

8. MARKETING AUTHORISATION NUMBER(S)
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
