Summary of Product Characteristics

1. Name of the Medicinal Product:
AXAPARA (Paracetamol Intravenous Infusion)

2. Qualitative and Quantitative Composition:
Qualitative Composition

Product Name: **AXAPARA**

Generic Name: Paracetamol Intravenous Infusion

Label Claim: Each 100 ml contains:

Paracetamol BP……..1.0% w/v

Water for Injections BP…….q.s.

3. Pharmaceutical Form
Intravenous Infusion
Description: Clear colorless solution

4. Clinical Particulars

4.1. Therapeutic indications
Paracetamol Intravenous Infusion is indicated for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by intravenous route 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 Posology

Intravenous use.

The 50 ml vial is restricted to term newborn infants, infants, toddlers and children weighing less than 33kg.

The 100 ml vial is restricted to adults, adolescents, and children weighing more than 33 kg.

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of paracetamol, solution for infusion (10mg/ml) per administration based on upper weight limits of group (ml)**	**Maximum Dose**
≤10 kg	7.5 mg/kg	0.75 mL/kg	7.5 ml	30 mg/kg
> 10 kg to ≤33kg	15 mg/kg	1.5mL/kg	49.5 ml	60mg/kg not exceeding 2g
> 33 kg to ≤50kg	15 mg/kg	1.5mL/kg	75 ml	60mg/kg not exceeding 3g
>50kg with additional risk factors for hepatotoxicity	1g	100mL	100 ml	3g
> 50 kg and no additional risk factors for hepatotoxicity	1g	100mL	100 ml	4g

Method of Administration

Take care when prescribing and administering Paracetamol intravenous infusion, to avoid dosing errors due to confusion between milligram (mg) and millilitre (ml), which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Take care to ensure the dose is measured and administered accurately.

The Paracetamol solution is administered as a 15-minute intravenous infusion.

Patients weighing ≤ 10 kg:

- The bottle of Paracetamol, solution for infusion, should not be hung as an infusion due to the small volume of the medicinal product to be administered in this population
- The volume to be administered should be withdrawn from the vial/bag

and diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Paracetamol, solution for infusion, into nine volumes diluent) and administered over 15 minute

- A 5 or 10 ml syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume. However, this should never exceed 7.5ml per dose
  The user should be referred to the product information for dosing guidelines

  Text for the 50ml and 100ml vials:
  To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.
  As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.

4.3. Contraindications

Paracetamol intravenous infusion is contraindicated:

- in patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients.
- in cases of severe hepatocellular insufficiency.

4.4. Special warnings and precautions for use

Warnings:
RISK OF MEDICATION ERRORS
Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death.
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 no other medicines containing paracetamol are administered at the same time.
Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage are not usually seen until two days, and up to a maximum of 4-6 days, after administration. Treatment with antidote should be given as soon as possible.

Precautions for use:
Paracetamol should be used with caution in cases of :

- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance $\leq$30 mL/min),
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration.

4.5. Interaction with other medicinal product 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 in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.
- Salicylamide may prolong the elimination t½ of paracetamol.
- Caution should be taken with the concomitant intake of enzyme-inducing substances.
- 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 show any malformation or foetotoxic effects.

Nevertheless, Paracetamol intravenous Infusion should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Lactation

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

4.7. Effects on ability to drive and use machines

Not relevant

4.8. Undesirable effects

As all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ System	**Rare >1/10000, <1/1000**	**Very rare <1/10000**
General	Malaise	Hypersensitivity reaction

Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Platelet/blood		Thrombocytopenia, Leucopenia, Neutropenia

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).
Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.
Cases of erythema, flushing, pruritus and tachycardia have been reported.

4.9. Overdose

There is a risk of poisoning, 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. Overdosing may be fatal in these cases.
Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain.
Overdose, 7.5 g or more of paracetamol in a single administration in adults or 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 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 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.
The treatment includes administration of the antidote, N-acetylcysteine (NAC) by the i.v. or oral route, if possible before the 10th hour. NAC can, however, give some degree of protection even after 10 hours, but in these cases prolonged treatment is given.

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 return of normal liver function. In very severe cases, however, liver transplantation may be necessary.

5. Pharmacological properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: other analgesics and antipyretics ATC Code: N02BE01

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

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

5.2. Pharmacokinetic Properties Adults

Absorption:

Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500mg and 1 g of Paracetamol Intravenous Infusion is similar to that observed following infusion of 1g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol Intravenous Infusion is about 15µg/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.

Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the cerebrospinal fluid at and after the 20th minute following infusion.

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 overdosing, 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 glucuronide (60-

80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Neonates, 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 neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

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, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance $\leq$ 30 mL/min), to increase the minimum interval between each administration to 6 hours.

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 special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of Paracetamol Intravenous Infusion in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

1. Pharmaceutical particulars

2. List of Excipients

Mannitol BP, Disodium Hydrogen Phosphate Dihydrate BP, Sodium Hydroxide BP, Water for Injections BP

3. Incompatibilities

This medicinal product should not be mixed with other medicinal products.

4. Shelf life

24 months from the date of manufacturing.

5. Special precautions for storage

Store below 30°C. Protect from light. Do not refrigerate or freeze.

6. Nature and contents of container

100 ml LDPE bottle packed in a Unit Carton, along with the pack insert.

7. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

To be administered aseptically. Discard any unused solution. To be used with a pyrogen free I.V administration set using aseptic technique.
For Intravenous Infusion only.
Keep medicine out of reach of children.

7. Marketing Authorization Holder

Axa Parenterals Limited
Plot No 936, 937& 939
Vill. Kishanpur, Jamalpur, Roorkee-247667
Distt. Haridwar (Uttarakhand), INDIA.
Telephone: +91-1332-234041/42/43
Telefax: +91-1332-234040
E-Mail: axapar@axapar.com

8. Marketing Authorization Number(s)

TAN 22 HM 0170

9. Date of first authorization/renewal of the authorization

04th May, 2022

10. Date of revision of the text