Summary of Product Characteristics

1. Name of Finished Pharmaceutical Product:

AXAPARA (Paracetamol Intravenous Infusion)

2. Qualitative and Quantitative Composition:

a) 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.

b) Quantitative Composition

Batch size: 750 Liters.

S. No	Name of Ingredients	Reference	Qty./ 100 ml	Function of Ingredient
1	Paracetamol	BP	1000 mg	Active ingredient
2	Mannitol	BP	5000 mg	Isotonic agent
3	Disodium hydrogen phosphate Dihydrate	BP	0.45 mg	Buffering agent
4	Sodium hydroxide	BP	q.s	pH adjustment
5	Hydrochloric acid	BP	q.s	pH adjustment
6	Water for Injections	BP	q.s.	Vehicle

3. Pharmaceutical Form

Solution for Infusion

Paracetamol Intravenous Infusion is A clear, colourless solution.

4. Clinical Particulars

4.1 Therapeutic indications

Paracetamol 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

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

The 50 ml vial is adapted to term new born infants, infants, toddlers and children weighing less than 33 kg.

Posology:

Dosing based on patient weight (please see the dosing table here below)

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol Intravenous infusion per administration based on upper weight limits of group (mL)	Maximum Daily 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
>50 kg with additional risk factors for hepatotoxicity	1g	100mL	100mL	3g
> 50 kg and no additional risk factors for hepatotoxicity	1g	100mL	100mL	4g

Method of administration:

Take care when prescribing and administering this medicinal product to avoid dosing errors due to confusion between milligram (mg) and milliliter (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.

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

Patients weighing ≤ 10 kg:

- The glass vial/bag 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 (see section 4.2).

It is recommended to use a suitable analgesic oral treatment as soon as this administration route 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 the recommended entails risk for 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 should be given as soon as possible (See section 4.9).

Precautions for use

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency, Gilbert's syndrome,
- severe renal insufficiency (creatinine clearance ≤30 mL/min),
- 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 t1/2 of paracetamol,
- Caution should be paid to the concomitant intake of enzyme-inducing substances (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 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 liver injury (including fulminant hepatitis, hepatic failure, 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. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, 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 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 hospitalization.
- Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.
- The treatment includes administration of the antidote, N-acetylcysteine (NAC), by the intravenous or oral route, if possible before the 10th hour. NAC can, however, give some degree 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 restitution of liver function. In very severe cases, however, liver transplantation may be necessary.

5. Pharmacological properties

5.1 Pharmacodynamics 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 24hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g of paracetamol is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of paracetamol is about 15 micrograms /mL and 30 micrograms /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 micrograms/mL) were observed in the Cerebro Spinal Fluid as and from the 20th minute following infusion.

Metabolism:

Paracetamol is metabolized mainly in the liver following two major hepatic pathways:

glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly storable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolized 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 in 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 longerthan 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.

Table. Age related pharmacokinetic values (standardized clearance, $*CL_{std}/F_{oral}$ ($l.h^{-1}$ 70 kg^{-1}), are presented below.

Age	**Weight (kg)**	**CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-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 years PNA	12	15.6
5 years PNA	20	16.3
8 years PNA	25	16.3

*CL_{std} is the population estimate for CL

Special populations

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 ≤ 30 mL/min), to increase the minimum interval between each administration to 6 hours (see section 4.2. Posology and method of administration).

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 in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

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

Mannitol BP, Disodium hydrogen phosphate Dihydrate BP, Sodium hydroxide BP, Hydrochloric acid BP & Water for Injection BP.

6.2 Incompatibilities

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

6.3 Shelf life

24 months from the date of manufacturing.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

100 ml LDPE bottle packed in a unit carton, along with the pack insert.

6.6 Special precautions/Instruction for disposal and other handling of use

Sterile, Non-pyrogenic Isotonic Single Dose Container.

To be administered aseptically Discard any unused solution immediately after use.

To be used with a pyrogen free I.V. administration set using aseptic technique.

Before administration, the product should be visually inspected for any particulate matter and discoloration.

The diluted solution should be visually inspected and should not be used in presence of opalescence, visible particulate matters or precipitate

7. Marketing Authorization Holder

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8. Marketing Authorization Number(s)

Not applicable

9. Date of first authorization/renewal of the authorization

Not applicable

10. Date of revision of the text

Not applicable