Summary of Product Characteristic

Benegan IV

1. Name of the Medicinal Product

Paracetamol 10 mg/mL Solution for infusion

2. Quality and Quantitative Composition

Each mL contains 10 mg paracetamol.

3. Pharmaceutical Form

Solution for infusion

4. Clinical Particulars

4.1 Therapeutic indication

Benegan IV 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 of hyperthermia and/or when other routes of administration are not possible.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Therapeutic indications, Accord-UK Ltd

4.2 Posology and method of administration

Intravenous use.

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

The 100 mL vial is restricted to adults, adolescents, and children weighing more 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 Benegan IV (10 mg/mL) per administration based on upper weight limits of group (mL)**	Maximum Daily Dose***
≤ 10 kg*	7.5 mg/kg	0.72 mL/kg	7.5 mL	30 mg/kg
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 mL/kg	49.5 mL	60 mg/kg not exceeding 2 g
> 33 kg to ≤ 50 kg	15 mg/kg	1.5 mL/kg	75 mL	60 mg/kg not exceeding 3 g
> 50 kg with additional risk factors for hepatoxicity	1 g	100 mL	100 mL	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	4 g

* Pre-term newborn infants: No safety and efficacy data are available for pre-term newborn infants (see section 5.2).

** Patients weighing less will require smaller volumes.

The minimum interval between each administration must be at least 4 hours. No more than 4 doses to be given in 24 hours.

The minimum interval between each administration in patients with severs renal insufficiency must be at least 6 hours.

*** Maximum daily dose: The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account.

Server renal insufficiency: 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 5.2).

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:

The maximum daily dose must not exceed 3 g (see section 4.4).

Method of administration

Take care when prescribing and administering, 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 prescription, 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 of paracetamol solution 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 and diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume paracetamol solution into nine volumes diluent) and administered over 15 minutes.
- 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 7.5 mL pre dose.
- The user should be referred to the product information for dosing guidelines.

Text for the 50 mL and 100 mL vials:

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the sport 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 infusion applies particularly for central route infusion, in order to avoid air embolism.

Text for the 50 mL vial:

Paracetamol of 50 mL vial can also be diluted in a 0.9% sodium chloride solution or 5 % glucose solution up to one tenth (one volume Paracetamol into nine volumes diluent) In this case, use the diluted solution within the hour following its preparation (infusion time included).

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Posology and method of administration, Accord-UK Ltd

4.3 Contraindications

Hypersensitivity to the active substance or the propacetamol hydrochloride (product of paracetamol) or to any of the excipients listed in section 6.1.

In cases of severe hepatocellular insufficiency.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Contraindications, Accord-UK Ltd

4.4 Special warnings and precautions for use

Warnings

RISK OF MEMICATION 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 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 either paracetamol or propacetamol.

Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms 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).

Text for the 50 mL and 100 mL vials:

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see section 4.2).

Precautions for use

Paracetamol should be used with caution in cases of:

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

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Special warnings and precautions for use, Accord-UK Ltd

4.5 Interaction with other medicinal products and other forms of interactions

- 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 (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.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Interaction with other medicinal products and other forms of interaction, Accord-UK Ltd

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding

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

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Interaction with other medicinal products and other forms of interaction, Accord-UK Ltd

4.7 Effects on ability to drive and use machine

Not relevant.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Effects on ability to drive and use machine, Accord-UK Ltd

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Organ System	Rare	Very rare
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.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Undesirable effects, Accord-UK Ltd

4.9 Overdose

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in your 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 adult or 140 mg/kg of body weight in a single administration in children, cause 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 blood sample for sample for plasma paracetamol assay, as soon as possible after the overdose.

The treatment includes administration of the antidote, N-acetylcystein (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, transplantation may be necessary.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Overdose, Accord-UK Ltd

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

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Pharmacodynamic properties, Accord-UK Ltd

5.2 Pharmacokinetics 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 500 mg and 1 g of paracetamol is similar to that observed following infusion of 1 g and 2 g propacetamol (containing 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 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.

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.

Biotransformation

Paracetamol is metabolized mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulfuric acid conjugation. The latter route is rapidly saturable 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 it 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 sulfate (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 sulfate conjugates than adults.

Table- Age related pharmacokinetic values (standardized clearance, *CLstd/Foral (L.h-1 70kg-1)

Age	Weight (kg)	CL_{std}/F_{oral} ($L.h^{-1}$ $70kg^{-1}$)
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 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 sulfate 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 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.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Pharmacokinetic properties, Accord-UK Ltd

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 solution 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.

Reference 1: SmPC, Paracetamol 10 mg/ml Solution for Infusion, Preclinical safety data, Accord-UK Ltd

6. Pharmaceutical Particulars

6.1 List of excipients

Sodium citrate dehydrate

Citric acid monohydrate

Sorbitol

Sodium sulfite anhydrous

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for dilution with 0.9% sodium chloride or 5% glucose solution.

6.3 Shelf life

2 years

Chemical and physical in use stability has been demonstrated for 6 hours at store below 30°C, after perforation of the rubber stopper.

Chemical and physical in use stability of the final diluted solution that has been produced under aseptic conditions has been demonstrated for 6 hours at store below 30°C.

However, for a microbiological point of view, the product should be use immediately.

6.4 Special precautions for storage

Store below 30 ºC. Protect from light. Store in the original package. Do not refrigerate or freeze.

6.5 Nature and contents of container

50 mL and 100 mL in clear glass vial (Type I) closed with rubber stopper and flip-off cap, packed or unpacked in a box of 1, 2, 5, 6, 10, 12 and 20 vials

6.6 Special precautions for disposal and other handling

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. Any unused solution should be discarded.

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

xx xxx/xx

9. Date of authorization

DD/MM/YYYY

10. Date of revision of the text

DD/MM/YYYY