1 NAME OF THE MEDICINAL PRODUCT

Paracetamol ALTAN 10 mg/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 10 mg paracetamol.

One 50 mL bag contains 500 mg paracetamol.

One 100 mL bag contains 1 g paracetamol.

Excipients with known effect:

One 50 mL bag contains 39.7 mg sodium (1.75 mmol) and 1.65 g glucose.

One 100 mL bag contains 79.4 mg sodium (3.5 mmol) and 3.30 g glucose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The solution is colourless or faintly straw-brown coloured

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol ALTAN 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

Intravenous use.

The 100 ml bag is restricted to adults, adolescents and children weighing more than 33 kg (approximately 11 years of age).

The 50 ml bag is adapted to term newborn 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 (10 mg/mL) per administration based on upper weight limits of group (mL)**	Maximum Daily Dose ***
≤10 kg *	7.5 mg/kg	0.75 mL/kg	7.5mL	30 mg/kg
> 10 kg to ≤33kg	15 mg/kg	1.5mL/kg	49.5mL	60mg/kg not exceeding 2g
> 33 kg to ≤50kg	15 mg/kg	1.5mL/kg	75 mL	60mg/kg not exceeding 3g

Patient weight	Dose per administration	Volume per administration	Maximum volume per administration **	Maximum Daily Dose ***
>50kg with additional risk factors for hepatotoxicity	1g	100mL	100mL	3g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100mL	100mL	4g

* 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 severe 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.

Severe renal insufficiency:

when paracetamol is administered to patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min), it is recommended to increase the minimum interval between administrations 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 PARACETAMOL ALTAN 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 an intravenous infusion.

The paracetamol solution is administered slowly, with an infusion time that must never be less than 15 minutes.

Patients weighing ≤ 10 kg:

• The plastic bag of Paracetamol ALTAN 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 bag and could be administered undiluted or diluted (from one to nine volumes diluent) in a 0.9% sodium chloride solution or 5% glucose solution and administered in 15-minute.

Use the diluted solution within the hour following its preparation (infusion time included).

• 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 bags:

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 plastic bags, 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.

Text for the 50ml bag:

Paracetamol ALTAN of 50ml bag can also be diluted in a 0.9% sodium chloride solution or 5% glucose solution (from one to nine volumes diluent). In this case, use the diluted solution within the hour following its preparation (infusion time included).

4.3 Contraindications

Paracetamol ALTAN is contraindicated in:

- patients with hypersensitivity to paracetamol, propacetamol hydrochloride (product of paracetamol) or to any of the excipients.

- cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Special 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 an oral analgesic treatment as soon as this route of administration is possible.

To avoid the risk of overdose, check that other medicinal products administered do not contain paracetamol.

Doses higher than those recommended carry a risk of very serious liver damage. Clinical signs and symptoms of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually seen after two days of drug administration with a peak seen usually after 4 - 6 days. Treatment with antidote should be administered as soon as possible (See section 4.9).

Text for the 50ml and 100ml bags:

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

Precautions for use

Paracetamol must 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 hepatic glutathione reserves)

- dehydration

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Important information about some ingredients of Paracetamol ALTAN

This medicinal product contains 3.5 mmol (79.4 mg) sodium per 100 mL, which should be taken into account by patients on a low salt diet.

This medicinal product contains 1.65 g glucose per 50 mL and 3.30 g glucose per 100 mL, which should be taken into consideration when treating patients with diabetes mellitus.

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 $t_{1/2}$ of paracetamol.

- Caution should be paid to the concomitant intake of enzyme-inducing substances (see section 4.9).

- Concomitant use of paracetamol (3 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.

- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant. 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. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

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 of foetotoxic effects. Nevertheless, Paracetamol ALTAN should only be used during pregnancy after a careful benefit-risk assessment. 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.

Lactation:

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported.

Consequently, Paracetamol ALTAN may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As with all products containing paracetamol, the adverse reactions are rare (≥1/10000, <1/1000) or very rare (<1/10000) and are listed below.

Organ system	Rare ≥1/10000, <1/1000	Very rare <1/10000
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased hepatic transaminase levels.	
Platelet/blood		Thrombocytopaenia, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 include 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 body weight in a single administration in children, causes hepatic cytolysis that will probably 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, which 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 to analyse plasma paracetamol as soon as possible after the overdose.

- Treatment includes administration of the antidote, *N*-acetylcysteine (NAC), intravenously or orally, if possible before 10 hours have passed. However, NAC can give some degree of protection even after 10 hours, but in these cases prolonged treatment should be administered.

- 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 ALTAN 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 ALTAN 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 intravenous administration of a single dose and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g 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 after intravenous infusion of 500 mg and 1 g paracetamol over 15 minutes is approximately 15 μg/ml and 30 μg/ml respectively.

Distribution

The volume of distribution for paracetamol is approximately 1 L/kg.

Paracetamol does not bind extensively to plasma proteins.

Following infusion of 1 g paracetamol, significant concentrations of paracetamol (approximately 1.5 μg/mL) were observed in cerebrospinal fluid after 20 minutes post-infusion.

Metabolism

Paracetamol is mainly metabolised in the liver via two main hepatic pathways: glucuronic acid conjugation and sulfuric acid conjugation. The latter route is rapidly saturable at doses exceeding 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 via 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. The plasma half-life is 2.7 hours and total body clearance is 18 L/h

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, which is slightly shorter (1.5 to 2 h) than in adults. In new-borns, the plasma half-life is longer than in infants at around 3.5 hours. Newborns, infants and children up to 10 years excrete significantly less glucuronide and more sulfate conjugates than adults. Total excretion of paracetamol and its metabolites is the same for all ages.

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

Age	*Weight (kg)*	*CLstd/Foral ($l.h^{-1}$ 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*

*CL_{std} is the population estimate for CL

Special populations:

Renal insufficiency

In cases of severe renal insufficiency (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. The elimination rate for the glucuronide and sulphate conjugates is three-times slower in subjects with severe renal insufficiency than in healthy subjects. Therefore, when paracetamol is administered to patients with severe renal insufficiency (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours (see section 4.2).

Elderly patients

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 confirmed 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

Glucose monohydrate.

Acetic acid.

Sodium acetate trihydrate.

Sodium citrate dihydrate.

Sodium hydroxide

Hydrochloric acid

Water for injections.

6.2 Incompatibilities

Paracetamol ALTAN should not be mixed with other medicinal products.

6.3 Shelf life

12 months for 100 ml bag

12 months for 50 ml bag

For single use.

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

Text for the 50ml bag:

If diluted in 0.9% sodium chloride or 5% glucose, the solution should also be used immediately. However, if the solution is not used immediately, do not store for more than 1 hour (infusion time included).

6.4 Special precautions for storage

Do not store above 25ºC.

Keep the bag in the protective overwrap in order to protect from light and excessive water loss. After opening the overwrapping immediate use is recommended.

6.5 Nature and contents of container

Ten 50 mL PVC bags with a metallised overwrapp

Twelve 50 mL PVC bags with a metallised overwrapp

Ten 100 mL PVC bags with a metallised overwrapp

Twelve 100 mL PVC bags with a metallised overwrapp

Fifty 100 ml PVC bags with a metallised overwrapp

6.6 Special precautions for disposal

Before administration, the product should be inspected visually for any particles and colour changes. For single use only. Any unused solution should be discarded.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For storage conditions after first opening of the medicinal product, see section 6.3.

7 MARKETING AUTHORISATION HOLDER

Altan Pharma Limited
The Lennox Building, 50 South Richmond Street
Dublin 2, D02FK02
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

46788/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/09/2022

10 DATE OF REVISION OF THE TEXT

14/01/2022