SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Accord 10 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each container contains 1000 mg paracetamol.
One ml contains 10 mg paracetamol
Excipients with known effect: Sodium 0.02 mg/ml
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear, free from visible particles and colourless to slightly brownish.

pH: 5.0-6.5

Theoretical Osm: 270-300 mOsm

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

Intravenous use.

The product 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 Paracetamol (10 mg/ml) per administration based on upper weight limits of group (ml)****	**Maximum Daily Dose ***
> 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 hepatotoxicity	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

*__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.
**__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.

Renal impairment
In patients with renal impairment, the minimum interval between each administration should be modified according to the following schedule:

Creatinine Clearance	Dosing Interval
cl ≥50 ml/min	4 hours
cl 10-50 ml/min	6 hours
cl <10 ml/min	8 hours

Hepatic impairment
In patients with chronic or compensated active hepatic disease, hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration, Gilbert's syndrome, weighing less than 50 kg: The maximum daily dose must not exceed 3 g (see section 4.4).

Elderly patients
No dose adjustment is usually required in geriatric patients.

Method of administration:

Take care when prescribing and administering Paracetamol 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.

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

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 pernfusion applies particularly for central route infusions, in order to avoid air embolism.

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 millilitre (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 other medicines (including prescription and nonprescription) administered do not contain either paracetamol or propacetamol.
Doses higher than the recommended entails risk for 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*).

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.

This medicinal product contains less than 1mmol sodium (23mg) per 100ml of Paracetamol, that is to say essentially 'sodium free'.

Paracetamol can cause serious skin reactions. Patients should be informed about the early signs of serious skin reactions, and the use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
As for all solutions for infusion presented in glass vials, 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, Gilbert's syndrome,
- severe renal insufficiency (see *sections 4.2 and 5.2*),
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione), anorexia, bulimia or cachexia,
- dehydration
- glucose-6-phosphatase dehydrogenase deficiency (may lead to haemolytic anaemia).

4.4 Special warnings and precautions for use

Warnings

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Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

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- chronic malnutrition (low reserves of hepatic glutathione), anorexia, bulimia or cachexia,
- dehydration
- glucose-6-phosphatase dehydrogenase deficiency (may lead to haemolytic anaemia).

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 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. These substances include, but are not limited to, barbiturates, isoniazid, carbamazepine, rifampin, and ethanol. (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.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic 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, a large amount of data from the use of oral therapeutic doses of paracetamol in pregnant women indicate neither malformative, nor fetal/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects. Nevertheless, Paracetamol Accord should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed..

Breastfeeding:

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. However, Paracetamol 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 paracetamol products, adverse drug reactions are common (≥1/100 to <1/10) or rare (>1/10,000 to <1/1,000) or very rare (<1/10,000) or have a not known frequency (cannot be estimated from the available data), they are described below :

System Organ Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Very rare	Thrombocytopenia Leucopenia, Neutropenia
Immune system disorders	Very rare	Anaphylactic shock* Hypersensitivity reaction*
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis
Cardiac disorders	Rare	Hypotension
	Not known	Tachycardia
Hepatobiliary disorders	Rare	Increased levels of hepatic transaminases
Skin and subcutaneous tissue disorders	Very rare	Rash* Urticaria* Serious skin reactions**
General disorders and administration site conditions	Rare	Malaise
	Common	Administration site reaction (pain and burning sensation)
	Not known	Erythema Flushing Pruritus

*Very rare cases of hypersensitivity reactions in the form of anaphylactic shock, urticaria, skin rash have been reported and require discontinuation of treatment.

**Very rare cases of serious skin reactions have been reported and require discontinuation of treatment.

Description of selected adverse reactions

High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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 the national reporting system via Yellow Card Scheme,Website: 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 comprise*:* 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 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 tube of blood sample for plasma paracetamol assay should be taken, 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 restitution of normal liver function. In very severe cases, however, liver transplantation may be necessary.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:* OTHER ANALGESICS AND ANTIPYRETICS

ATC Code: N02BE01

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

Phamacodynamic effects
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.

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 500 mg and 1 g of Paracetamol is similar to that observed following infusion of 1g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol 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.

Biotransformation
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 P_{450} 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.

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

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 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 (see section 4.2.), the minimum interval between each administration should be increased to 6 hours (see section 4.2.).

Elderly:

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population (see section 4.2).

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 i.v. 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.

Paracetamol was found to be noncarcinogenic in male rats as well as in male and female mice. Equivocal evidence of carcinogenic activity was noted for female rats based on an increased incidence of mononuclear cell leukemia.

A comparative review of the literature on paracetamol genotoxicity and carcinogenicity showed that genotoxic effects of paracetamol appear only at dosages above the recommended range resulting in severe toxic effects including pronounced liver and bone marrow toxicity. The threshold level for genotoxicity is not reached at therapeutic dosages of paracetamol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium dihydrogen phosphate dihydrate
Povidone K-12
Sodium Hydroxide– for pH adjustment
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vials: 36 months.
Plastic bags: 18 months.

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

Glass vials: Do not refrigerate or freeze. Store in the original package in order to protect from light.
Plastic bags: Do not store above 25ºC. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Clear type II glass vials of 100 ml closed with halogenated butyl rubber stopper and aluminium cap. Pack size: 1, 10, 12 and 20 vials.

Polyolefin plastic bags of 100 ml, provided with one or two polypropylene ports (closed with a polyisoprene rubber stopper and sealed with a polypropylene cap) with metalized PET/PE or metalized PET/PP/PE overpouch. Pack size: 10, 12 and 50 bags.
Not all pack sizes may be marketed.

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.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House, 319, Pinner Road
North Harrow, Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/1170

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

03/02/2025