PZ16713/05

Product Information

Paracetamol-AFT

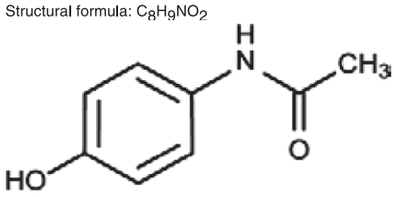
NAME OF THE MEDICINE

Paracetamol-AFT Solution for Infusion 10mg/ml
(Paracetamol)

DESCRIPTION

Paracetamol-AFT (paracetamol) solution for infusion is a clear to slightly yellowish solution. It contains 10mg/mL of paracetamol. Paracetamol is a white crystalline solid or powder chemically described as 4–acetamidophenol. It is soluble in water (1 in 70), soluble in alcohol (1 in 7), acetone (1 in 13), glycerol (1 in 40), propylene glycol (1 in 9) and also soluble in solutions of the alkali hydroxides.

Structural formula: $C_8H_9NO_2$



Molecular weight: 151.2

Paracetamol-AFT solution for infusion contains 10mg/mL of paracetamol (100mL vial contains 1g of paracetamol)

Paracetamol-AFT solution for infusion contains excipients mannitol, cysteine hydrochloride monohydrate, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid, water for injections (100mL vial contains 7.6mg of sodium)

PHARMACOLOGY

PHARMACODYNAMICS
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-AFT 10mg/mL, solution for 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-AFT 10mg/mL, solution for infusion reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

PHARMACOKINETICS
Adults
Absorption:
Paracetamol pharmacokinetics is linear up to 2g after a single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500mg and 1g of Paracetamol-AFT is similar to that observed following infusion of 1g and 2g propacetamol (containing 500mg and 1g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1g of Paracetamol-AFT is about 15µg/ml and 30µg/ml respectively

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

Paracetamol is not extensively bound to plasma proteins.

Following infusion of 1g paracetamol, significant concentrations of paracetamol (about 1.5µg/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 18L/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 2h) 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 (standardized clearance,$CL_{std/Foral}$ ($l.h^{-1}$ $70kg^{-1}$), are presented below.*

Age	*Weight (kg)*	*$CL_{std/Foral}$ ($l.h^{-1}$ $70kg^{-1}$)*
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 10-30mL/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 (creatinine clearance ≤ 30mL/min), the minimum interval between each administration should be increased to 6 hours (see DOSAGE AND ADMINISTRATION).

Elderly subjects:
The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

INDICATION

Paracetamol-AFT 10mg/mL, solution for 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.

DOSAGE AND ADMINISTRATION

Intravenous route

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

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol-AFT (10mg/mL) per administration**	Maximum Daily Dose***
>50kg with additional risk factors for hepatotoxicity	1g	100mL	100mL	3g
> 50kg and no additional risk factors for hepatotoxicity	1g	100mL	100mL	4g

Note:

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

** 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:
It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30mL/min), to increase the minimum interval between each administration to 6 hours (See PHARMACOKINETICS).

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:
The maximum daily dose must not exceed 3g (see WARNINGS AND PRECAUTIONS).

Method of administration

Take care when prescribing and administering Paracetamol-AFT 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. Take care to ensure the dose is measured and administered accurately.

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

Patients weighing ≤10kg:

- The glass vial/bag of Paracetamol-AFT 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 or bag and could be administered undiluted or diluted, up to one tenth (one volume Paracetamol-AFT into 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 10ml 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.

To remove solution, use a 0.8mm 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.

CONTRAINDICATIONS

Paracetamol-AFT 10mg/mL solution for 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

WARNINGS AND PRECAUTIONS

WARNING:

This preparation contains PARACETAMOL.
Do not take any other paracetamol containing medicines at the same time.

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 DOSAGE AND ADMINISTRATION).

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 administered do not contain either paracetamol or propacetamol.

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 to 6 days. Treatment with antidote should be given as soon as possible (see OVERDOSE AND TREATMENT).

This medicinal product contain less than 1mmol sodium (23mg) per 100ml of Paracetamol-AFT, i.e. essentially "sodium free".

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see DOSAGE AND ADMINISTRATION)

Precautions
Paracetamol-AFT should be used with caution in cases of:
- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance ≤ 30mL/min) (see DOSAGE AND ADMINISTRATION, AND PHARMACOKINETICS)
- chronic alcoholism
- chronic malnutrition (low reserves of hepatic glutathione).
- dehydration

Allergy alert: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away.

DRUG INTERACTIONS

- 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 OVERDOSE AND TREATMENT)
- Concomitant use of paracetamol (4g 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 one week after paracetamol treatment has been discontinued.

USE IN 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-AFT should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

USE IN LACTATION

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

ADVERSE REACTIONS

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.

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.

Cases of erythema, flushing, pruritus and tachycardia have been reported.

OVERDOSE AND TREATMENT

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 of nausea, vomiting, anorexia, pallor and abdominal pain. Overdose, 7.5 g or more of paracetamol in a single administration in adults or 140mg/kg of body weight in a single administration in children, causes hepatitis cytolytic 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 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 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.

INCOMPATIBILITIES

Paracetamol-AFT should not be mixed with other medicinal products.

PRESENTATION

Paracetamol-AFT 10mg/mL solution for infusion is available in 100mL clear glass vials in a pack size of 10 vials.
One 100mL vial contains 1g of paracetamol. The solution is clear to slightly yellowish.

STORAGE AND SHELF LIFE

Store below 30°C.

Do not refrigerate or freeze.

Paracetamol-AFT 10mg/ml, Solution for Infusion should be kept in its marketing packaging, the carton box, protected from light and should be only taken out at the moment of use.

Shelf-life: 2 years.

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.

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)

Special precautions for disposal

Use 0.8mm needle and vertically perforate the stopper at the spot specifically indicated.

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

Malaysia Registration Number: MAL14085010ACZ

PRODUCT OWNER, REGISTRATION HOLDER

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