PZ17215/02

NAME OF THE MEDICINE
Paracetamol-AFT 10mg/mL Solution for Infusion

DESCRIPTION
Paracetamol-AFT 10mg/mL Solution for Infusion is a clear, colourless to slightly yellowish solution. Paracetamol-AFT 10mg/mL Solution for Infusion contains 10mg/ml of Paracetamol (100 mL vial contain 1 g of Paracetamol).

INDICATIONS
Paracetamol-AFT 10mg/mL Solution for Infusion is indicated for the relief of mild to moderate pain and the reduction of fever where an intravenous route of administration is considered clinically necessary.

CONTRAINDICATIONS
Paracetamol-AFT 10mg/ml Solution for Infusion is contraindicated:

- In cases of hypersensitivity to Paracetamol or to propacetamol hydrochloride (prodrug of Paracetamol) or to any of the excipients,
- In cases of severe hepatocellular insufficiency
- In patients with hepatic failure or decompensated active liver disease

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 Paracetamol.

Doses higher than the recommended entail a risk of very serious liver damage. Clinical symptoms and signs of liver damage are usually seen first after two days with a maximum usually after 4 to 6 days. Treatment with antidote should be given as soon as possible (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS
Paracetamol-AFT should be used with caution in cases of:

- Hepatocellular insufficiency
- Severe renal insufficiency (creatinine clearance ≤30 mL/min)
- Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia).
- Chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day)
- Anorexia, bulimia or cachexia; chronic malnutrition (low reserves of hepatic glutathione)
- Dehydration, hypovolemia

(See DOSAGE AND ADMINISTRATION)

The total dose of Paracetamol should not exceed 4 g per day for patients weighing 50 kg or more. 60mg/kg for patients weighing 50kg or less and more than 33kg (without exceeding 3 g), 60mg/kg for patients weighing 33kg or less and more than 10kg (without exceeding 2 g) and 30mg/kg for patients weighing 10kg or less. It is important to consider the contribution of all Paracetamol containing medications, including non-prescription, oral or PR forms of the drug to this total daily Paracetamol dose prior to administering Paracetamol-AFT. If the daily dose of Paracetamol from all sources exceeds the maximum, severe hepatic injury may occur (See OVERDOSE).

Hepatic injury
Patients with hepatic insufficiency, chronic alcoholism, chronic malnutrition or dehydration may be at a higher risk of liver damage following administration of Paracetamol-AFT.

Effects on Fertility
Intravenous Paracetamol (administered as propacetamol) had no effect on fertility of rats at systemic exposure levels (based on AUC) greater than twice those anticipated at the maximum clinical dose.

Use in pregnancy

Category A
Paracetamol has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

The reproductive toxicity of IV Paracetamol has not been directly tested in animal studies. IV administration of maternotoxic doses of the pro-drug, propacetamol, to pregnant rats and rabbits during organogenesis increased the incidence of extranumerary ribs and sacral vertebrae (normal variations in these species) at 0.7-fold (rabbits; mg/m² basis) and 7-fold (rats; AUC basis) the maximum anticipated clinical exposure to Paracetamol. The clinical significance of these findings is not known. No signs of pre/ post-natal toxicity were observed in rats treated with IV propacetamol at maternal exposures (based on AUC) greater than 3-fold those anticipated at the maximum clinical dose.

Nevertheless, Paracetamol-AFT should only be used during pregnancy after a careful benefit-risk assessment. In pregnant patients, 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. No sign of toxicity were observed in rat pups of dams that received IV propacetamol postpartum at maternal exposures (based on AUC) greater than twice those anticipated at the maximum clinical dose. Paracetamol-AFT may be used in breast-feeding women, but caution should be observed.

Genotoxicity
Paracetamol was not mutagenic in the bacterial mutagenicity assay, but it was clastogenic in mammalian cell assay systems in vitro (mouse TK, human lymphocyte) and in a mouse micronucleus assay *in vivo*.

The clastogenic effect was dose-dependent, and the mechanism appears to involve inhibition of replicative DNA synthesis and ribonucleotide reductase at above threshold doses. The clinical significance of clastogenic findings is equivocal as positive findings *in vivo* only occurred at exposures (ca. 8 times the maximum anticipated clinical exposure, based on c_{max}) greater than that for hepatotoxicity, and at doses that were associated with significant cytotoxicity.

Carcinogenicity
No evidence of carcinogenic potential was observed for Paracetamol in long-term oral studies in mice (up to 3000 mg/m²/day, similar to human exposure) and male rats (up to 1800 mg/m²/ day, 0.7 times human exposure). Equivocal evidence of carcinogenic potential (mononuclear cell leukaemia) was observed only in female rats at 1900 mg/m²/day, or 0.7 times the maximum anticipated clinical exposure on a mg/m² basis.

INTERACTIONS WITH OTHER MEDICINES
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 t½ of paracetamol.

Caution should be taken with the concomitant intake of enzyme-inducing substances (see OVERDOSE). 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.

ADVERSE EFFECTS
The overall incidence of adverse events in intravenous Paracetamol-treated patients compared to placebo within the clinical trial set can be observed in the tables below:

Adverse Events in Adults- greater than 1% (observed in the clinical trial set)

	IV Paracetamol % (n=99)	Placebo % (n=102)
Neurological		
Dizziness	2.7	2.9
Headache	1.3	4.9
Dystonia		
Gastrointestinal		
Vomiting	4.0	2.9
Dry mouth		
Diarrhoea	1.3	
Constipation	6.7	11.8
Nausea	10.0	8.8
Dyspepsia	1.3	
Enlarged abdomen	2.0	
Gastrointestinal disorders NOS	2.0	
Haematological		
Anaemia	2.7	6.9
Post-operative haemorrhage	2.0	
Hepatobiliary		
Gamma GT-increase	1.3	
SGPY- increase	1.3	
Psychiatric		
Insomnia		1.96
Skin and Appendage		
Injection site pain	2.0	
Injection site reaction	2.67	
Post-operative site reaction	2.67	
Pruritus	3.3	4.9
Respiratory		
Alveolitis	1.3	2.94
Coughing	2.0	
Endocrine/ Metabolite		
Hyperglycaemia	1.3	
Hypokalaemia	1.3	
General		
Fatigue	1.59	
Fever		5.9
Oedema - peripheral		
Chest pain	1.33	

Adverse Events in Children - greater than 1% (observed in the clinical trial set)

	IV Paracetamol % (n=95)
Skin and Appendage Injection site pain Injection site reaction	14.74
Neurological Hypotonia	1.05
Gastrointestinal Nausea Vomiting Abdominal pain Eructation	1.05 5.26
Body as a Whole Fever	1.05

As with 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)	Isolated reports
General	Malaise	Hypersensitivity reaction	
Cardiovascular	Hypotension	Shock	
Liver	Increased level of hepatic transaminases		
Platelet/ Blood	Agranulocytosis, neutropenia		Thrombocytopenia
Neurological		Neurological disorders	Coma
Renal/ Genitourinary		Acute renal failure	
Skin and Appendage	Macular rash, injection site reaction	Maculo-papular rash, pemphigoid reaction, pustular rash	Lyell syndrome

Post Market Adverse Effects for Propacetamol/Paracetamol
The following adverse events have also been reported during post-marketing surveillance, but incidence rate (frequency) is not known.

Organ System	Adverse Events
Blood and the lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Nausea Vomiting
General disorders and administration site conditions	Administration site reaction
Hepatobiliary disorders	Fulminant hepatitis Hepatic necrosis Hepatic failure Hepatic enzymes increased
Immune system disorders	Angioneurotic (Quincke's) edema Anaphylactic shock Anaphylaxis Hypersensitivity reactions (ranging from simple skin rash or urticaria to anaphylactic shock) have been reported and require the discontinuation of treatment
Skin and subcutaneous tissue disorders	Erythema Flushing Pruritus Rash Urticaria

DOSAGE AND ADMINISTRATION

The prescribed dose must be based on the patient's weight.

Unintentional overdose can lead to serious liver damage and death (see OVERDOSE). Healthcare providers are reminded that it is essential to follow both the weight-related dose recommendations and to consider individual patient risk factors for hepatotoxicity including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration (see DOSAGE AND ADMINISTRATION - Hepatic impairment).

It is recommended that a suitable oral analgesic treatment be substituted for Paracetamol-AFT as soon as the patient can be treated by oral route (see CONTRAINDICATIONS).

Intravenous route
Paracetamol-AFT 10mg/mL Solution for Infusion should not be mixed with other medicinal products. Use of the 100mL vial is restricted to adults, adolescents and children weighing more than 33kg.

Dosage:
Dosing is based on patient weight. Dosing recommendations are presented in the table below

Patient Weight	Paracetamol dose (10mg/mL) per administration	Minimum interval between each administration	Maximum daily dose#
>50kg	1 g (i.e. one 100mL vial) Up to 4 times per day	4 hours*	≤4 g Must not exceed 4 g in 24 hours
>33kg and ≤50kg	15mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	4 hours*	≤60mg/kg, without exceeding 3 g Must not exceed 3g in 24 hours

* The minimum interval between each administration must be 4 hours in patients without hepatic or renal impairment. However, in patients with renal and/ or hepatic impairment the minimum interval between doses must not be less than 6 hours.

The maximum daily dose takes into account all medicines containing Paracetamol or propacetamol.

** No safety and efficacy data are available for premature neonates. There is limited data on the use of Paracetamol-AFT in neonates and infants <6 months of age.

Hepatic impairment
In patients with chronic or compensated active hepatic disease, especially those with hepatocellular insufficiency, chronic malnutrition (low reserves of hepatic glutathione), and dehydration, the dose should not exceed 3 g/day.

Method of administration
The Paracetamol solution is administered as a 15-minute intravenous infusion; it contains no antimicrobial agent, and is for single use in one patient only.

Paracetamol-AFT 10mg/mL Solution for Infusion can be diluted in a 0.9% Sodium Chloride or 5% Glucose solution up to one tenth. In this case, use the diluted solution within the hour following its preparation (infusion time included).

As for all solutions for infusions in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of the administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.

It is recommended that for the administration of Paracetamol-AFT 10mg/mL Solution for Infusion a syringe or giving set with a diameter equal to or below 0.8 mm should be used for solution sampling. In addition, it is recommended that the bung is pierced at the location specifically designed for needle introduction (where the thickness of the bung is lowest). If these recommendations are not adhered to the likelihood of bung fragmentation or the bung being forced into the vial is increased.

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 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 cytolytic hepatitis likely to induce complete and irreversible hepatic necrosis, resulting in acute or fulminant hepatic failure, 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 blood sample 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 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 the liver function. In very severe cases, however, liver transplantation may be necessary.

Storage
Store below 25°C.
Do not refrigerate or freeze. Protect from light
Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. The product should be used immediately after opening and any unused solution should be discarded.

If diluted in 0.9% Sodium Chloride or 5% Glucose, the solution should be used immediately. However, if the solution is not used immediately, store below 25°C for a maximum of one hour (infusion time included).

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