La Nuova Grafica Lucana srl
ITALY

ISTRUZIONI PIEGATE

SCHEDA DATI TECNICI

Cliente S.M. Farmaceutici s.r.l. **Codice cliente** 110.00002

Prodotto Paracetamol-AFT - Istr. piegate

Cod. prodotto PZ16952/01 rev. 01

Carta g/m^2 50

Colori		Pantone N.	Stampa	
			in bianca	in volta
1	Nero		☑	☐
2	Nero		☐	☑

Formato steso mm 300 x mm 210

Formato piegato mm 105 x mm 50

Note: _____

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Data _____ *Data* _____

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La N.G.L. Controllo Qualità firma Cliente per approvazione

APPROVED
By Vijahyakumar at 12:37 pm, Jan 16, 2019

Product Information

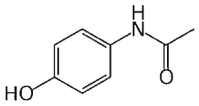
PARACETAMOL-AFT (Paracetamol) SOLUTION FOR INFUSION 10mg/mL

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

DESCRIPTION

PARACETAMOL-AFT (paracetamol) solution for infusion is a clear and 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 1 g of paracetamol)

PARACETAMOL-AFT solution for infusion contains mannitol, cysteine hydrochloride monohydrate, dibasic sodium phosphate dihydrate, sodium hydroxide, hydrochloric acid, water for injections.

PHARMACOLOGY

PHARMACODYNAMICS

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

PHARMACOKINETICS

Adults

Absorption:

Paracetamol pharmacokinetics is linear after a single administration of up to 2 g and after repeated administration during 24 hours.

For 1g intravenous paracetamol, peak plasma concentration is obtained as and from the end of infusion. The maximum plasma concentration (Cmax) of paracetamol observed following intravenous infusion of 1 g intravenous paracetamol 10 mg/mL is about 30 µg/mL. About 15 minutes is required to obtain the maximal plasma concentration (T max).

Distribution

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

Paracetamol is not extensively bound to plasma proteins.

Following infusion of 2g proparacetamol, (equivalent to 1g of paracetamol) significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the cerebrospinal fluid 20 minutes after 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 poisoning, the quantity of this toxic metabolite is increased.

At therapeutic doses, CYP3A4, the major isoform of P450 in human liver, contributes to the production of the cytotoxic metabolite. For very high, supratherapeutic plasma concentrations (1500 mg/ L) of paracetamol, the 2E1 and 1A2 isoforms may also be involved

Elimination:

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 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 and Infants <6 months of age

Clinical Trials examining the pharmacokinetics of intravenous paracetamol in neonates and infants <6 months of age are limited. The safety and efficacy of intravenous paracetamol in premature neonates hasnot been established.

In neonates, the plasma half-life is longer than in infant's i.e. around 3.5 hours. Neonates and, infants excrete significantly less glucuronide and more sulphate conjugates than adults. The potential effect of immaturity in metabolic and elimination pathways of paracetamol should be considered when administering paracetamol to neonates and children <6 months of age.

Infants and children >6 months of age

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

Special populations

Renal Impairment

Paracetamol should be administered with caution to patients with renal impairment. In cases of severe renal impairment (creatinine clearance ≤ 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. It is recommended that there be an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Paracetamol should be administered with caution to patients with hepatic impairment. Hepatic impairment may decrease the clearance of paracetamol or increase the probability of hepatic toxicity.

Elderly subjects

There was a significant increase in AUC and reduction in clearance of paracetamol and its metabolites in elderly subjects. However, these statistically significant differences were not likely to be clinically relevant during short-term infusions. Hence, no dose adjustment is required in this population.

INDICATIONS

PARACETAMOL-AFT 10 mg/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 10 mg/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 ADMINSTRATION).

PRECAUTIONS

PARACETAMOL-AFT should be used with caution in cases of:

- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance ≤ 30 mL/min) (see DOSAGE AND ADMINISTRATION AND PHARMACOKINETICS)
- Glucose 6 Phosphate Dehyrogenase (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.

The total dose of paracetamol should not exceed 4 g per day. It is important to consider the contribution of all paracetamol containing medications, including non-prescription, oral or PR (parenteral) 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)

Rarely, paracetamol may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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.

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.

Caution should be paid to the concomitant intake of enzyme-inducing agents. These substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, carbamazepine and ethanol. Induction of metabolism of paracetamol from enzyme inducers may result in an increased level of hepatotoxic metabolites.

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 one week after paracetamol treatment has been discontinued.

Phenytoin administered concomitantly may result in decreased paracetamol effectiveness and an increased risk of hepatotoxicity. Patients receiving phenytoin therapy should avoid large and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity.

Busulfan – busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with paracetamol may result in reduced busulfan clearance.

Diflunisal – concomitant diflunisal increases paracetamol plasma concentrations and this may increase hepatotoxicity.

Carcinogenicity and Mutagenicity

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 Cmax) greater than that for hepatotoxicity, and at doses that were associated with significant cytotoxicity.

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.

Use in 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 fetus.

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.

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-AFT 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

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 lactation

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. No signs 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. Consequently, PARACETAMOL-AFT 10 mg/mL, solution for infusion may be used in breast-feeding women.

APPROVED
By Vijahyakumar at 12:38 pm, Jan 16, 2019

ADVERSE REACTIONS
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	
SGPT - 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	14.74
Injection site reaction	
Neurological	
Hypotonia	1.05
Gastrointestinal	
Nausea	1.05
Vomiting	5.26
Abdominal pain	
Eructation	
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

DOSAGE AND ADMINISTRATION
Intravenous route
PARACETAMOL-AFT 10 mg/mL, solution for infusion should not be mixed with other medicinal products.

Dosage:
Adults
The recommended dose in patients weighing more than 50kg is:
Paracetamol 1g per administration, i.e. one 100 mL vial, up to four times a day.

The recommended dose in patients weighing less than 50kg and more than 33kg is: Paracetamol 15mg/kg per administration (1.5mL solution per kg) up to four times a day.

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

For adults weighing from 33 to 50kg the maximum daily dose from all sources of paracetamol must not exceed 60mg/kg.

Use of 100mL vial is restricted to adults, adolescents and children weighing more than 33kg.

Hepatic Impairment
In patients with chronic or compensated active hepatic disease, especially those with hepatocelluar insufficiency, chronic malnutrition (low reserves of hepatic glutathione), and dehydration, the dose should not exceed 3g/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 also 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 infusion presented 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 0.8mm 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 the 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 poisoning, 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. Poisoning may be fatal in these cases. Acute overdose with paracetamol may also lead to acute renal tubular necrosis.

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 140 mg/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.

The Rummack-Matthews nomogram relates plasma levels of paracetamol and the time after oral ingestion to the predicted severity of liver injury. The relation of parental paracetamol levels in overdose to liver toxicity has not been examined. Advice or treatment protocols based on oral paracetamol overdoses may not accurately predict the incidence of liver toxicity or need for antidote therapy in PARACETAMOL-AFT overdose.

Emergency measures
- Immediate hospitalisation.
- Before beginning treatment, take blood for plasma paracetamol assay, as soon as possible after the overdose.
- Treatment of paracetamol overdose may include the antidote N-acetyl cysteine (NAC) by the IV or oral route. In overdoses of oral paracetamol NAC is administered, if possible, before 10 hours but may give some degree of protection form liver toxicity even after this time. The optimal time for administration of NAC and necessary duration of therapy have not been established for overdoses of PARACETAMOL-AFT.
- 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.

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

STORAGE
Store below 30°C.
Do not refrigerate or freeze.
Store in the outer carton in order to 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

Shelf-life: 2 years.

If diluted in 0.9% Sodium Chloride or 5% Glucose, the solution should be used immediately. However, if the solution is not used immediately, do not store for more than one hour (infusion time included).

REGISTRATION NUMBER
Singapore
1g in 100mL SIN14692P

PRODUCT OWNER
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DATE OF REVISION
Date of revision in Singapore: December 2018 v1