1 PARACETAMOL-AFT SOLUTION FOR INJECTION

Paracetamol 10mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10mg paracetamol.
One 50ml vial contains 500mg of paracetamol
One 100 ml vial contains 1000mg of paracetamol

Excipients with known effect
Mannitol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

PARACETAMOL-AFT (paracetamol) solution for infusion is a clear, colourless to slightly yellowish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

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

Unintentional overdose can lead to serious liver damage and death (see section 4.9). 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 section 4.2 - 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 section 4.3).

Intravenous route
PARACETAMOL-AFT 10 mg/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 33 kg.

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

Patient Weight	Paracetamol dose (10 mg/mL) per administration	Minimum interval between each administration	Maximum daily dose #
> 50 kg	1 g (i.e. one 100 mL vial) Up to 4 times per day	4 hours *	≤ 4 g Must not exceed 4 g in 24 hours
> 33 kg and ≤ 50 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	4 hours *	≤ 60 mg/kg, without exceeding 3 g Must not exceed 3 g in 24 hours
> 10 kg and ≤ 33 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	6 hours	≤ 60 mg/kg, without exceeding 2 g Must not exceed 2 g in 24 hours
≤ 10 kg **	7.5 mg/kg (i.e. 0.75 mL solution per kg) The volume must not exceed 7.5 mL per dose Up to 4 times per day	6 hours	≤ 30 mg/kg Must not exceed 30 mg/kg 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 (see section 5.2).

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 administrationThe 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 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 10 mg/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 the lowest). If these recommendations are not adhered to the likelihood of bung fragmentation or the bung being forced into the vial is increased.

Paediatric Patients

PARACETAMOL-AFT should not be hung as an infusion due to the small volume of the product to be administered in the paediatric population.

To avoid dosing errors in neonates and infants (≤ 10 kg) and confusion between milligrams (mg) and millilitres (mL), it is recommended to specify the intended volume for administration in millilitres (mL). The volume of PARACETAMOL-AFT (10 mg/mL) administered should never exceed 7.5 mL per dose in this weight group. In neonates and infants (≤ 10 kg), very small volumes will be required. A 5 mL or 10 mL syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume.

For paediatric dosing, the 50 mL vial of Paracetamol-AFT can be diluted using either a 0.9% sodium chloride solution or a 5% glucose solution up to one-tenth dilution (one volume paracetamol injection into nine volumes diluent). The diluted solution must be used within one hour following its preparation (infusion time included).

4.3 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.

4.4 Special warnings and precautions for use

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

• hepatocellular insufficiency,

• severe renal insufficiency (creatinine clearance ≤ 30 mL/min)

• 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. for patients weighing 50 kg or more, 60 mg/kg for patients weighing 50 kg or less and more than 33 kg (without exceeding 3 g), 60 mg/kg for patients weighing 33 kg or less and more than 10 kg (without exceeding 2 g) and 30 mg/kg for patients weighing 10 kg 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 section 4.9).

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.

4.5 Interaction with other medicines 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.

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.

4.6 Fertility, pregnancy and lactation

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 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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable 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	
SGPT - increase	1.3	
Psychiatric		
Insomnia		1.96
Skin and Appendage		4.9
Injection site pain	2.0	
Injection site reaction	2.67	
Post-operative site reaction	2.67	
Pruritus	3.3	
Respiratory		
Alveolitis	1.3	2.94
Coughing	2.0	
Endocrine/Metabolite		
Hyperglycaemia	1.3	
Hypokalaemia	1.3	
General		
Fatigue	1.59	5.9
Fever		
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	
Abdominal pain	5.26
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

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 Event
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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://nzphvc.otago.ac.nz/reporting/

4.9 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 from 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

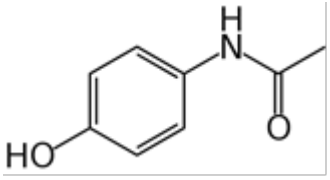
5.1 Pharmacodynamic properties

PARACETAMOL-AFT (paracetamol) solution for infusion 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

CAS Number: 103-90-2

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

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 a duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacokinetic properties

Adults

Absorption:

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

The bioavailability of paracetamol following infusion of 1 g of Paracetamol-AFT 10mg/mL is similar to that observed following infusion of 2 g propacetamol (containing 1 g paracetamol). For both these products, peak plasma concentration is obtained as and from the end of infusion. The maximum plasma concentration (C_{max}) of paracetamol observed following intravenous infusion of 1 g Paracetamol-AFT 10 mg/mL is about 30 µg/mL. About 15 minutes is required to obtain the maximal plasma concentration (T_{max}).

The bioavailability of paracetamol following infusion of 500 mg of Paracetamol-AFT 10 mg/mL, solution for infusion is similar to that observed following infusion of 1g propacetamol (containing 500mg paracetamol). The maximum plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg of Paracetamol-AFT 10 mg/mL, solution for infusion is about 15 µg/mL.

The pharmacokinetics of oral paracetamol (500mg) and intravenous propacetamol (1g) were compared in a randomised, double-blind, 2-period crossover study in 12 healthy male subjects. As expected, plasma concentrations of intravenous propacetamol were significantly higher and obtained earlier, compared to oral administration, however after the first hour and up to 24 hours the plasma concentrations remained similar. (Fig. 1 & Table 1 below).

Fig 1:

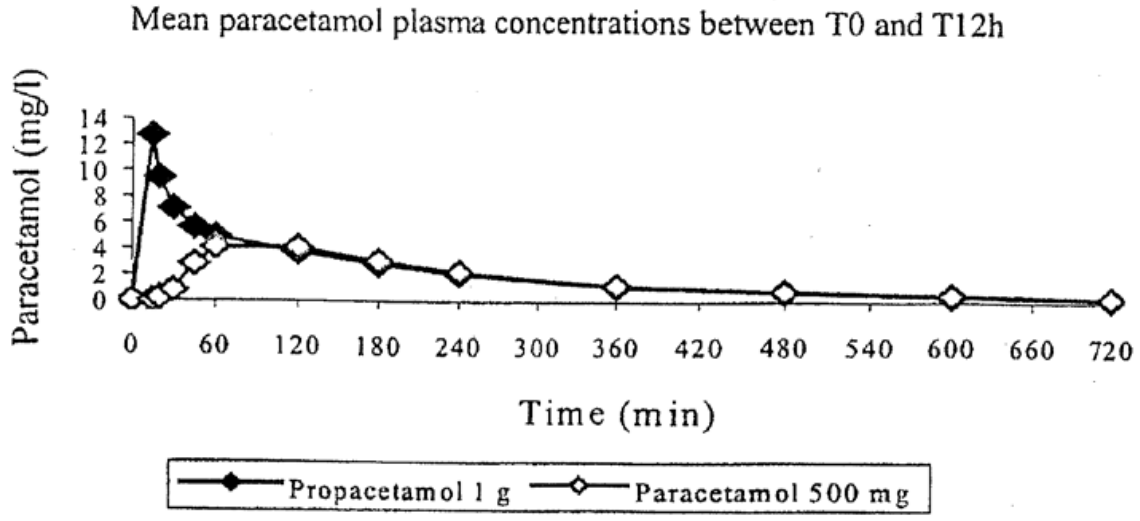


Table 1

Pharmacokinetic parameters of paracetamol (mean ± sd)

	Propacetamol 1g i.v. (n = 12)	Paracetamol 500mg oral (n = 12)	n value
Cmax (µg/ml)	12.72 ± 3.51	5.49 ± 1.89	p < 0.0001
Tmax (h)	0.25	1.46 ± 0.57	p < 0.0001
t1/2 (h)	3.60 ± 1.07	3.17 ± 0.41	NS
AUC_{0-12h}	24.07 ± 3.77	19.48 ± 3.69	p < 0.0001
$AUC_{0-\infty}$	25.5 ± 4.27	21.04 ± 4.49	p < 0.0001
Cl (l/h/kg)	0.28 ± 0.04	-	-
Vd (l/kg)	1.29 ± 0.37	-	-
F	-	82 ± 9.4	-
F: bioavailability of oral paracetamol (500mg) versus intravenous propacetamol (1g). Cmax: plasma concentration at the end of infusion.			

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

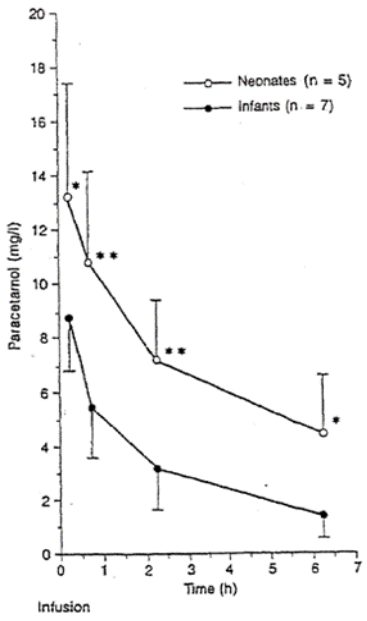
Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive 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 has not been established. In a trial of 12 children between 1 and 232 days of age, which included 5 children less than 10 days of age the pharmacokinetic results for paracetamol solution for infusion were as follows:

Fig 2:



Paracetamol concentrations (means ± SD) versus time after a 15-min propacetamol infusion. * $p < 0.05$, ** $p < 0.01$, differences between groups.

Table 2
Pharmacokinetic parameters of all children and of children aged less than and over 10 days

	Total	**<10 days**	**>10 days**	**P**
t½, h	2.7 (1.0)	3.5 (0.5)	2.1 (0.9)	<0.05
AUC, µg/L/h	41.3 (25.9)	64.0 (23.7)	25.0 (10.9)	<0.01
CL, L/kg/h	0.275 (0.2)	0.149 (0.067)	0.365 (0.219)	<0.05
V, L/kg	0.8 (0.2)	0.7 (0.2)	0.9 (0.1)	NS
Results are expressed as means with SD in parentheses. t½ = elimination half-life, AUC = area under the curve, CL = total body clearance of drug from plasma, V = volume of distribution				

The infants in the study were aged between 1-232 days (mean 88±95 days). In the neonates aged less than 10 days, the gestational age was 37.4±3.9 weeks (32-41.3 weeks). The weight of the neonates at the time of the study was 2.578±0.959 kg (1-3.8); birth weight was 2.578±1.022 kg (1-3.920 kg). The mean administered dose was 15.3±mg/kg (13.4-20 mg/kg).

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 section 4.2).

Hepatic Impairment

Paracetamol should be administered with caution to patients with hepatic impairment (see sections 4.3 and 4.4). 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.

CLINICAL TRIALS

Clinical trials were performed with two different formulations of paracetamol, paracetamol and propacetamol. Propacetamol 2g is equivalent to paracetamol 1g. Refer to section 4.2 for the correct dosing instruction for Paracetamol-AFT.

Analgesia - Adults

Two phase III studies were conducted to compare the safety and analgesic efficacy of IV paracetamol and propacetamol in 303 adults. Two accepted acute pain models, i.e. orthopaedic surgery pain and oral surgery pain were used to evaluate analgesic efficacy.

Efficacy of IV paracetamol for the treatment of postoperative pain following orthopaedic surgery

One hundred and fifty one patients were included in this study; 49 patients were administered paracetamol IV 1g and 52 patients placebo. The groups of patients were comparable with regard to demographic and baseline characteristics. One hundred and thirty seven (90.7%) of patients received 4 administrations over 24 hours, 2 (1.3%) patients received 3; 2 (1.3%) patients received 2 and 10 (6.6%) patients received only 1 administration.

The primary measured efficacy endpoint parameter of the trial was the evaluation of paracetamol 1g versus placebo after single dose-pain relief scores (PID, PRID, maxPR, maxPID, SPID, TOTPAR, time to peak effects and time to first rescue medication; numbers and proportion of patients requiring rescue medication (PCA-morphine); patients global evaluation (PGA).The secondary measured efficacy endpoint parameter was paracetamol IV 1g versus placebo after repeated doses.

An overview of the results are shown in Tables 3a and b:

Table 3a

Overview of analgesic efficacy criteria – single dose evaluation – ITT population

	Inj APAP (n=50)	Pbo (n=52)	P value APAP/Pbo
TOTPAR Mean SD	 6.6 5.9	 2.2 3.8	0.0001
SPID Mean SD	 2.3 3.6	 -0.6 3.5	0.0001
SPAID Mean SD	 104.7 112.9	 -27.7 92.4	0.0001
SPRID Mean SD	 9.0 8.7	 1.6 6.2	0.0001

Table3a cont'd

	Inj APAP (n=50)	Pbo (n=52)	P value APAP/Pbo
MAXPR Mean SD	 2.0 1.4	 0.9 1.1	0.0001
MAXPID Mean SD	 1.0 0.8	 0.4 0.8	0.0001
MAXPAID Mean SD	 36.6 23.4	 11.9 20.0	0.0001
MAXPRID Mean SD	 3.0 2.1	 1.3 1.8	
Median time to rescue medication (h) [95% CI]*	3.0 [1.4;4.0]	0.8 [0.6;1.1]	0.0001
*CI – Confidence Interval: Inj APAP – injectable paracetamol; Pbo - placebo			

Table 3b

Overview of repeated-dose efficacy criteria – ITT population

	Inj APAP 1 g	Pbo	p-value (APAP/Pbo)
Quantity of rescue medication (mg of equivalent morphine dose) over 24 h			
N Mean SD	48 38.33 35.14	52 57.41 52.3	0.0007
Number of requested administrations of rescue medication over 24 h			
N Mean SD	48 47.4 39.1	51 89.3 94.5	0.0003
Actual number of administrations of rescue medication over 24 h			
N Mean SD	48 27.7 20.2	52 42.3 26.0	0.0001
MPI (T0-T24)			
N Mean SD	46 1.4 0.5	47 1.6 0.6	0.0202
MPAI (T0-T24)			
N Mean SD	46 31.6 17.0	47 39.6 18.5	0.0006
Composite endpoint MPI (T0-T14 h)			
N Mean SD	45 -25.3 91.7	47 33.1 95.4	0.0004
Composite endpoint MPAI (T0-T14 h)			
N Mean SD	45 -25.3 91.7	47 37.8 91.4	0.0001
Patient's global evaluation adjusted for rescue medication use (at 24 h)			
N Mean SD	49 81.6 42.8	52 61.8 37.3	0.0019

Efficacy of IV paracetamol for the treatment of postoperative pain following oral (post dental) surgery

One hundred and fifty two patients were included in this study; 51 patients were administered paracetamol IV 1g and 50 patients placebo. The groups of patients were comparable with regard to demographic and baseline characteristics.

The primary measured efficacy endpoint parameter of the trial was the evaluation of paracetamol IV 1g versus placebo after single dose-pain relief scores (PID, PRID, maxPR, maxPID, SPID, TOTPAR, time to peak effects and time to first rescue medication; numbers and proportion of patients requiring rescue medication (PCA-morphine); patients global evaluation (PGA).The secondary measured efficacy endpoint parameter was paracetamol 1g versus placebo after repeated doses.

An overview of the results are shown in Table 4.

Table 4

	Inj APAP 1 g (n=51)	Pbo (n=50)	p-value (APAP/Pbo)
TOTPAR Mean SD	 6.9 5.9	 1.7 3.4	0.0001
SPID Mean SD	 2.2 3.1	 -0.4 2.9	0.0001
SPAID Mean SD	 88.1 109.3	 -12.4 86.0	0.0001
SPRID Mean SD	 9.1 8.6	 1.4 5.5	0.0001
MAXPR Mean SD	 2.3 1.0	 1.0 1.2	0.0001
MAXPID Mean SD	 1.1 0.5	 0.3 0.6	0.0001
MAXPAID Mean SD	 32.9 15.6	 11.0 16.4	0.0001
MAXPRID Mean SD	 3.4 1.4	 1.3 1.7	0.0001
t-MAXPR Median [95% CI]	 0.25 NE	 0.25 NE	0.5557
t-MAXPID Median SD	 0.25 NE	 0.25 NE	0.7167
t-MAXPAID Median SD	 0.5 [0.25;0.5]	 0.25 NE	0.283
t-MAXPRID Median SD	 0.25 NE	 0.25 NE	0.5557
Median time to onset (min) [95%CI]	 8.0 [5.0;12.0]	 NE	0.0001

Median time to rescue medication (h) [95% CI]	2.1 [1.4;3.4]	0.7 [0.5;0.8]	0.0001
CI=confidence interval; NE=not estimable; Inj APAP= injectable paracetamol; Pbo=placeb0			

Analgesia - Children

Efficacy of IV paracetamol with postoperative pain (hernia repair)
One hundred and eighty three patients were included in this study, of which 95 patients were administered paracetamol IV 15 mg/kg. The groups of patients were comparable with regard to demographic and baseline characteristics.

The primary measured efficacy endpoint parameter of the trial was the evaluation of pain intensity difference (PID) on VAS (investigator rated) at 15, 30 minutes, 1, 2, 3, 4, 5 and 6 hours post-dose. The secondary measured efficacy endpoint parameter for the trial

was PID on the objective pain scale (OPS), pain relief rated by the investigator, SPID-OPS, SPID-VAS, TOTPAR, number of children with VAS score ≤ 15mm, investigators global evaluation, time to remedication, changes from baseline in HR, SBP and DBP.

An overview of the results are shown in Tables 5 and 6.

Table 5

Mean scores of pain intensity difference (PID) – VAS (investigator) – ITT population								
Treatment	T 15 min	T 30 min	T 1 h	T 2 h	T 3 h	T 4 h	T 5 h	T 6 h
Patient number	95	95	95	95	95	95	95	95
Inj Paracetamol	25.6	38.1	38.8	40.4	41.3	40.3	41.0	40.9
SD	20	22.1	22.8	22.9	23.7	24.0	23.9	24.1
P value (b)	0.7944	0.5373	0.1990	0.6196	0.624	0.8397	0.5125	0.5569
Mean scores of pain intensity difference – VAS (Child) – ITT population								
Patient number	45	45	45	45	45	45	45	45
Inj Paracetamol	20.8	31.7	34.3	36.4	38.8	39.1	39.1	39.6
SD	27.9	29.2	26	25.5	28.7	28.6	28.7	28.6
P value (b)	0.4327	0.9125	0.9275	0.6239	0.9265	0.8965	0.9194	0.6182
Mean scores of pain intensity difference – OPS – ITT population								
Patient number	95	95	95	95	95	95	95	95
Inj Paracetamol	2.3	3.5	3.7	3.7	4.0	3.9	3.9	4.0
SD	2.8	2.9	3.2	3.0	3.1	3.1	3.1	3.1
P value (b)	0.9218	0.9488	0.4667	0.6266	0.2553	0.2548	0.1900	0.1307
Mean scores of pain relief – ITT population								
Patient number	95	95	95	95	95	95	95	95
Inj Paracetamol	2..4	3.2	3.2	3.3	3.4	3.3	3.4	3.4
SD	1.3	1.2	1.2	1.2	1.2	1.2	1.2	1.2
P value (b)	0.8181	0.5833	0.5540	0.2613	0.1972	0.3599	0.1834	0.1267

(b) PR=BLPI=centre=TRT BLPI: baseline pain intensity (VAS inverstigator); TRT: treatment

Table 6

Measure of analgesic efficacy: Area under the curves over 6 h (mean score±sd) Intent to treat population

		Treatment group n=95	
	Statistics	Inj APAP	P value
TOTPAR	Mean SD	19.7 6.6	0.2568*
SPID-OPS	Mean SD	22.8 17.5	0.3223*
SPID-VAS (investigator)	Mean SD	239.4 132.6	0.7582*
SPID-VAS (child)	Mean SD	223.3 152.2	0.7649*

*Analysis of covariance

Antipyrexia

Propacetamol is a different formulation than paracetamol IV which delivers 1g of paracetamol for every 2g of propacetamol administered.

Antipyretic efficacy & safety of a single administration of 30 mg/kg of intravenous propacetamol in children (age 3 to 12 years) with acute fever of infectious origin

Forty one children with acute fever (ear temperature between 38.5 °C to 41 °C) of infectious origin. The groups of patients were comparable with regard to demographic and baseline characteristics.

The primary measured efficacy endpoint parameter of the trial was to evaluate the antipyretic efficacy of a single intravenous dose of 30 mg/kg of propacetamol (equivalent to 15mg/kg paracetamol IV 1g) in comparison with placebo in children with acute fever of infectious origin (changes in body temperature (BT) from 0.5 hours to 6 hours post dose)

The secondary measured efficacy endpoint parameter was the evaluation of the percentage of body temperature reduction from baseline at each evaluation time, weighted sum of changes in body temperature over the TO-T4 and TO-T6 periods, weighted sum of percentages of body temperature reduction over the TO-T4 and TO-T6 periods. Time to reach body temperature below 38 °C over the TO-T6 period. Number and percentage of children with a BT below 38 °C over the TO-T6 period. Maximum value of changes in body temperature and time to occurrence after TO. Vital signs (respiratory rate, heart rate, arterial blood pressure): changes over time after dosing. Investigator's global evaluation. Time to re-medication (with calculation of time at which 50% of children require re-medication) over the TO-T6 period, number and percentage of children requiring rescue medication over the TO-T6 period. Safety - vital signs & adverse events.

An overview of the results are shown in Tables 7 and 8

Table 7

Primary criterion: mean body temperature change from baseline of 6 h

Treatment	T30 min	T1 h	T2 h	T3 h	T4 h	T5 h	T6 h
Propacetamol							
Mean	0.4	1.0	1.4	1.6	1.6	1.4	
SD	0.3	0.5	0.6	0.6	0.8	0.9	
n	20	20	19	19	19	18	
Placebo							
Mean	0.1	0.1	0.1	0.0	0.0	-0.1	
SD	0.4	0.5	0.6	0.7	0.8	0.8	
n	21	21	20	18	14	10	
Treatment p=value (b)	0.0009	0.0001	0.0001	0.0001	0.0001	0.0002	
Treatment* centre p=value (c)	0.8713	0.5719	0.4979	0.5606	0.3843	0.9323	
(b) Response=BL bodytemp+centre=trt; (c) Response=BL bodytemp+centre+trt+(trt*centre) + (trt*bodytemp)							

Table 8

Overview of secondary efficacy criteria

	Propacetamol (n = 20)	Placebo (n = 21)	p-value
Time to first remedication over 6hr (hr)(median)	Not.est.	5.0	0.0046
Nb pts receiving ≥ 1 rescue med. N (%)	2 (10%)	11 (52.4%)	0.004
Time to reach BT < 38°C over 6hr (hr)(median)	2.0	Not.est.	0.0001
Nb pts reaching at least once BT<38°C over 6hr n (%)	18 (90%)	5 (23.8%)	0.001
Max BT-change from baseline over 6hr (°C)	2.0 ± 0.7	0.6 ± 0.6	0.0001
T-max BT-change over 6hr (hr)(median)	3.0	2.0	0.0316
Weighted sum of BT-changes over 6hr (°C.hr)	7.9 ± 3.8	-0.1 ± 3.6	0.0001
Weighted sum of BT-changes over 4hr (°C.hr)	5.2 ± 2.0	0.2 ± 2.2	0.0001
Weighted sum of % of BT-reduction over 6hr (%.hr)	390 ± 170	-20 ± 190	0.0001
Weighted sum of % of BT-reduction over 4hr (%.hr)	260 ± 90	0 ± 130	0.0001
BT reduction at T0.5 (%)	20 ± 20	0 ± 20	0.0007
BT reduction at T1 (%)	50 ± 20	0 ± 30	0.0001
BT reduction at T2 (%)	70 ± 30	0 ± 40	0.0001
BT reduction at T3 (%)	80 ± 20	0 ± 40	0.0001
BT reduction at T4 (%)	80 ± 40	0 ± 40	0.0001
BT reduction at T5 (%)	70 ± 40	10 ± 50	0.0001
BT reduction at T6 (%)	60 ± 60	-10 ± 40	0.0003
All values are expressed as the mean ± SD unless otherwise stated			

5.3 Preclinical safety data

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 Cmax) 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cysteine hydrochloride monohydrate
Dibasic sodium phosphate dihydrate
Hydrochloric acid
Mannitol
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

PARACETAMOL-AFT is available as packs of 10 x 50 mL or 10 x 100 mL glass vials

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33.203
Takapuna
Auckland
Email:customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

12/07/2012

10 DATE OF REVISION OF THE TEXT

06 September 2018

SUMMARY TABLE OF CHANGES

Date	**Section(s) Changed**	**Change (s)**
06 September 2018	All	Reformat consistent with new Medsafe Data Sheet Template.