AUSTRALIAN PRODUCT INFORMATION – PARACETAMOL IV PFIZER® (paracetamol)

1. NAME OF THE MEDICINE

Paracetamol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of PARACETAMOL IV PFIZER contains paracetamol 10 mg.

Paracetamol is a white crystalline solid or powder. 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.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for infusion.

PARACETAMOL IV PFIZER is a colourless or faintly straw-brown coloured solution.

PARACETAMOL IV PFIZER contains 10 mg/mL of paracetamol (50 mL bag contains 500 mg of paracetamol; 100 mL bag contains 1 g of paracetamol).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARACETAMOL IV PFIZER 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

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 a day.	4 hours [*]	≤ 4g 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 IV PFIZER in neonates and infants <6 months of age (see section 5.2 Pharmacokinetic properties).

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 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 section 4.2 Dose and method of administration, Hepatic Impairment).

It is recommended that a suitable oral analgesic treatment be substituted for paracetamol as soon as the patient can be treated by oral route (see section 4.3 Contraindications).

Method of Administration

Intravenous Route

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

PARACETAMOL IV PFIZER should not be mixed with other medicinal products.

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

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. The product should be used immediately after opening and any unused solution should be discarded.

PARACETAMOL IV PFIZER 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, 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 IV PFIZER 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.

Dosage Adjustment

Hepatic Impairment

In patients with impaired hepatic function, the dose must be reduced or the dosing interval prolonged. The maximum daily dose should not exceed 60 mg/kg/day (not exceeding 2 g/day) in the following situations:

- adults weighing less than 50 kg
- chronic or compensated active hepatic disease, especially those with mild to moderate hepatocellular insufficiency
- Gilbert's syndrome (familial hyperbilirubinaemia)
- chronic malnutrition (low reserves of hepatic glutathione)
- dehydration

Paediatric Patients

PARACETAMOL IV PFIZER 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 IV PFIZER (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 bag of PARACETAMOL IV PFIZER 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 IV PFIZER 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, and reach a maximum usually after 4 to 6 days. Treatment with antidote should be given as soon as possible (see section 4.2 Dose and method of administration).

4.4 Special warnings and precautions for use

PARACETAMOL IV PFIZER should be used with caution in cases of:

- Hepatic insufficiency (see Use in Hepatic Impairment)
- Renal insufficiency (see Use in Renal Impairment)
- 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 sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

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 IV PFIZER. If the daily dose of paracetamol from all sources exceeds the maximum, severe hepatic injury may occur (see section 4.9 Overdose).

Paracetamol can cause serious skin reactions such as acute generalised 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.

High Anion Gap Metabolic Acidosis

Caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.

After co-administration of flucloxacillin and paracetamol, close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including testing of urinary 5-oxoproline.

Use in Hepatic Impairment

Patients with hepatic insufficiency, chronic alcoholism, chronic malnutrition or dehydration may be at a higher risk of liver damage following administration of PARACETAMOL IV PFIZER.

PARACETAMOL IV PFIZER should be used with caution in cases of hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia).

See section 4.3 Contraindications.

Use in Renal Impairment

PARACETAMOL IV PFIZER should be used with caution in cases of severe renal insufficiency (creatinine clearance ≤30 mL/min).

Use in the Elderly

See section 5.2 Pharmacokinetic properties.

Paediatric Use

The safety and efficacy of paracetamol solution for infusion in premature neonates has not been established. There is limited data on the use of PARACETAMOL IV PFIZER in neonates and infants <6 months of age (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of 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 coumarin anticoagulants including warfarin 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.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors.

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 PARACETAMOL IV PFIZER 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/m^2 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.

Premature constriction/closure of the fetal ductus arteriosus has been reported following *in utero* exposure to paracetamol. In most of these reports, exposure to paracetamol occurred during the third trimester of pregnancy.

Nevertheless, PARACETAMOL IV PFIZER 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. Rash in nursing infants has 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. PARACETAMOL IV PFIZER may be used in breast-feeding women, but caution should be observed.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The overall incidence of adverse events in paracetamol solution for infusion-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)

Adverse Event	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 disorder 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		

Adverse Event	Paracetamol % (n = 99)	Placebo % (n = 102)
Alveolitis	1.3	2.94
Coughing	2.0	
Endocrine/Metabolic		
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)

Adverse Event	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:

System Organ Class	Rare >1/10000, <1/1000	Very Rare <1/10000	Isolated Reports
General and administration site condition	Malaise	Hypersensitivity reaction	
Cardiovascular	Hypotension	Shock	
Hepatobiliary disorders	Increased levels of hepatic transaminases		
Blood and the lymphatic system disorders	Agranulocytosis, neutropenia		Thrombocytopenia
Neurological		Neurological disorders	Coma
Renal/Genitourinary		Acute renal failure	
Skin and subcutaneous tissue disorders	Macular rash, injection site reaction	Maculo-papular rash, pemphigoid reaction, pustular rash	Lyell Syndrome

Post Marketing Adverse Events for Propacetamol/Paracetamol

The following adverse events have also been reported during post-marketing surveillance, but incidence rate (frequency) is not known.

System Organ Class	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	- Steven's Johnson syndrome (SJS) - Toxic epidermal necrolysis (TEN) - Acute generalised exanthematous pustulosis (AGEP) - Erythema - Flushing - Pruritus - Rash - Urticaria
Metabolism and nutrition disorders	- Rare cases of high anion gap metabolic acidosis, when paracetamol is used concomitantly with flucloxacillin, generally in the presence of risk factors.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 Rumack-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 IV PFIZER overdose.

Methaemoglobinaemia has been reported in cases of paracetamol 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 8 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 solution for infusion.
- 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.

Adults: keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised by a doctor.

Children and adolescents: keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.

If an **overdose** is taken or suspected, go to a hospital straightaway even if you feel well because of the risk of delayed, serious liver damage.

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

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

PARACETAMOL IV PFIZER 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 IV PFIZER reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

Clinical Trials

Clinical trials were performed with two different formulations of paracetamol, paracetamol solution for infusion and propacetamol. Propacetamol 2 g is equivalent to paracetamol solution for infusion 1 g. Refer to section 4.2 for the correct dosing instructions for PARACETAMOL IV PFIZER.

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.

All the studies presented were phase III, randomised, double-blind, active- and/or placebo-controlled. The studies were well conducted according to the GCP guidelines with ethics approval. Treatment compliance was good in all the studies.

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 solution for infusion 1 g 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 solution for infusion 1 g versus placebo after single dose-pain relief scores pain intensity difference (PID), pain relief intensity difference (PRID), maximum pain relief (maxPR), maximum pain intensity difference (maxPID), sum of the pain intensity difference (SPID), total pain relief (TOTPAR), time to peak effects and time to first rescue medication; numbers and proportion of patients requiring rescue medication (patient controlled analgesia (PCA)-morphine); patients global evaluation (PGA). The secondary measured efficacy

endpoint parameter was paracetamol solution for infusion 1g versus placebo after repeated doses.

An overview of the results are shown in Tables 1a and 1b.

[Table 1a] 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
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	 0.0001
Median time to rescue medication (hr) [95% CI]*	3.0 [1.4;4.0]	0.8 [0.6;1.1]	0.0001

* CI - Confidence interval; Inj. APAP - injectable acetaminophen; Pbo - placebo

[Table 1b] 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 24h			
N	48	52	
Mean	38.33	57.41	0.0007
SD	35.14	52.3	
Number of requested administrations of rescue medication over 24h			
N	48	51	
Mean	47.4	89.3	0.0003
SD	39.1	94.5	
Actual number of administrations of rescue medication over 24h			
N	48	52	
Mean	27.8	42.3	0.0001
SD	20.2	26.0	
MPI (T0-T24hr)			
N	46	47	
Mean	1.4	1.6	0.0202
SD	0.5	0.6	
MPAI (T0-T24hr)			
N	46	47	
Mean	31.6	39.6	0.0006
SD	17.0	18.5	
Composite endpoint MPI (T0-T24hr)			
N	45	47	
Mean	-25.3	37.8	0.0001
SD	91.7	91.4	
Patient's global evaluation adjusted for rescue medication use (at 24hr)			
N	49	52	
Mean	81.6	61.8	0.0019
SD	42.8	37.3	

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 solution for infusion 1 g 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 solution for infusion 1 g 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 solution for infusion 1 g versus placebo after repeated doses.

An overview of the results are shown in Table 2.

[Table 2]

	Inj. APAP 1g n=51	**Pbo n=50**	**p-value APAP/Pbo**
TOTPAR			
Mean	6.9	1.7	0.0001
SD	5.9	3.4	
SPID			
Mean	2.2	-0.4	0.0001
SD	3.1	2.9	
SPAID			
Mean	88.1	-12.4	0.0001
SD	109.3	86.0	
SPRID			
Mean	9.1	1.4	0.0001
SD	8.6	5.5	
MAXPR			
Mean	2.3	1.0	0.0001
SD	1.0	1.2	
MAXPID			
Mean	1.1	0.3	0.0001
SD	0.5	0.6	
MAXPAID			
Mean	32.9	11.0	0.0001
SD	15.6	16.4	
MAXPRID			
Mean	3.4	1.3	0.0001
SD	1.4	1.7	
t-MAXPR			
Median	0.25	0.25	0.5557
[95% CI*]	NE**	NE	
t-MAXPID			
Median	0.25	0.25	0.7167
[95% CI]	NE	NE	
t-MAXPAID			
Median	0.5	0.25	0.283
[95% CI]	[0.25; 0.5]	NE	
t-MAXPRID			
Median	0.25	0.25	0.5557
[95% CI]	NE	NE	
Median time To onset (min)	8.0	NE	0.0001
[95% CI]	[5.0. 12.0]		
Median time to rescue medication (hr)	2.1	0.7	0.0001
[95% CI]	[1.4; 3.4]	(0.5; 0.8)	

*CI: confidence interval; **NE: not estimable; Inj APAP: injectable acetaminophen; Pbo: Placebo

Analgesia - Children

<u>Efficacy of IV paracetamol with postoperative pain (hernia repair)</u>

One hundred and eighty three patients were included in this study, of which 95 patients were administered paracetamol solution for infusion 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 visual analogue scale (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 ≤ 15 mm, investigators global evaluation, time to remedication, changes from baseline in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

An overview of the results are shown in Tables 3 and 4.

[Table 3] Mean Scores of Pain Intensity Differences (PID) – VAS (Investigator) – ITT Population

Treatment	***T15 min***	***T30 min***	***T1 h***	***T2h***	***T3h***	***T4h***	***T5h***	***T6h***
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

(b) PID = BLPI + center + TRT; BLPI = Baseline Pain Intensity (VAS-investigator); TRT = Treatment

Mean Scores of Pain Intensity Differences – VAS (Child) – ITT Population

Treatment	***T15 min***	***T30 min***	***T1 h***	***T2h***	***T3h***	***T4h***	***T5h***	***T6h***
Patient Number	45	45	45	45	45	45	45	45
Inj. Paracetamol	20.8	31.7	34.4	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

(b) PID = BLPI + center + TRT; BLPI = Baseline Pain Intensity (VAS-investigator); TRT = Treatment

Mean Scores of Pain Intensity Differences – OPS – ITT Population

Treatment	***T15 min***	***T30 min***	***T1 h***	***T2h***	***T3h***	***T4h***	***T5h***	***T6h***
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

(b) PID = BLPI + center + TRT; BLPI = Baseline Pain Intensity (OPS); TRT = Treatment

Mean Scores of Pain Relief – ITT Population

Treatment	***T15 min***	***T30 min***	***T1 h***	***T2h***	***T3h***	***T4h***	***T5h***	***T6h***
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=center=TRT BLPI: Baseline Pain Intensity (VAS investigator); TRT: Treatment

[Table 4]

Measure of analgesic efficacy: Area-under-the-curves over 6 hr (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*

*Analyse of covariance

Antipyrexia

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

Antipyretic efficacy and 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 38.5ºC to 41ºC) 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 15 mg/kg paracetamol solution for infusion) 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 T0-T4 and T0-T6 periods; weighted sum of percentages of body temperature reduction over the T0-T4 and T0-T6 periods; time to reach body temperature below 38°C over the T0-T6 period; number and percentage of children with a BT below 38°C over the T0-T6 period; maximum value of changes in body temperature and time to occurrence after T0; 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 T0-T6 period; number and percentage

of children requiring rescue medication over the T0-T6 period; safety: vital signs & adverse events.

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

[Table 5] Primary criterion: mean body temperature change from baseline of 6hr

Treatment	T30 min	T1 hr	T2 hr	T3 hr	T4 hr	T5 hr	T6 hr
Propacetamol							
Mean	0.4	1.0	1.4	1.6	1.6	1.4	1.2
SD	0.3	0.5	0.6	0.6	0.8	0.9	1.2
n	20	20	19	19	19	18	18
Placebo							
Mean	0.1	0.1	0.1	0.0	0.0	-0.1	-0.1
SD	0.4	0.5	0.6	0.7	0.8	0.9	0.8
n	21	21	20	18	14	11	10
Treatment p=value (b)	0.0009	0.0001	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	0.5141	0.9323
(b) Response = BLbodytemp + centre + trt; (c) Response = BLbodytemp + centre + trt + (trt*centre) + (trt*BLbodytemp)							

[Table 6] 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
Number of patients receiving ≥1 rescue med. n (%)	2 (10%)	11 (52.4%)	0.004
Time to reach BT <38ºC over 6hr (hr) (median)	2.0	Not.est.	0.0001
Number of patients reaching at least once BT <38ºC over 6hr n (%)	18 (90%)	5 (23.8%)	0.001
Max BT-change from baseline over 6hr (ºC)	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 (ºC.hr)	7.9±3.8	-0.1±3.6	0.0001
Weighted sum of BT-changes over 4hr (ºC.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.

5.2 Pharmacokinetic properties

Adults

Absorption

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

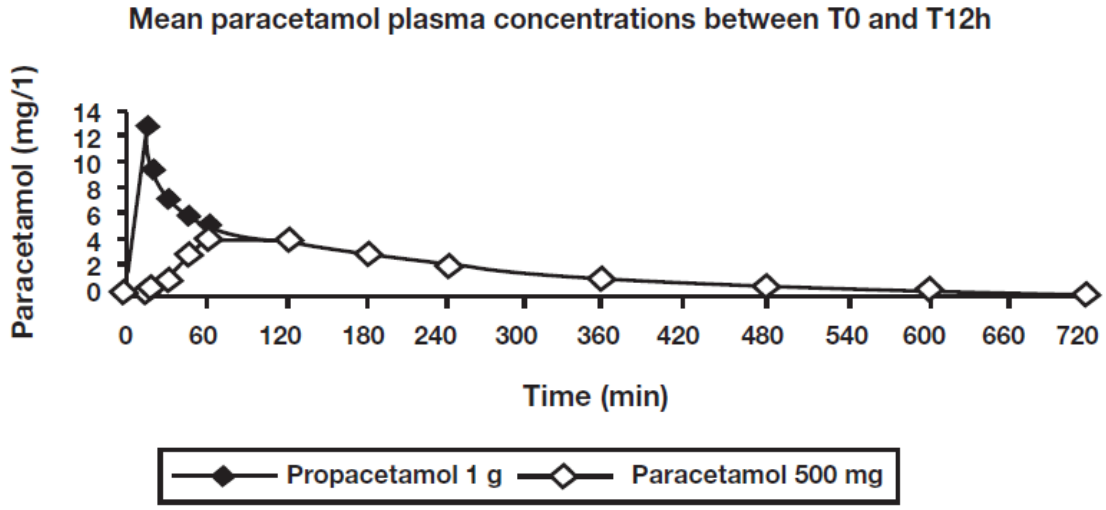
The bioavailability of paracetamol following infusion of 1 g of paracetamol solution for

infusion 10 mg/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 solution for infusion10 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 10 mg/mL solution for infusion is similar to that observed following infusion of 1g propacetamol (containing 500 mg paracetamol). The maximum plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg of paracetamol10 mg/mL solution for infusion is about 15 µg/mL.

The pharmacokinetics of oral paracetamol (500 mg) and intravenous propacetamol (1 g) 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 (**Figure 1 and Table 7 below**).

[Figure 1]



[Table 7]

Pharmacokinetic parameters of paracetamol (mean ± sd)

	Propacetamol 1 g - i.v. (n = 12)	Paracetamol 500 mg - 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 (500 mg) versus intravenous propacetamol (1 g).
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 2 g propacetamol, (equivalent to 1 g 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.

Excretion

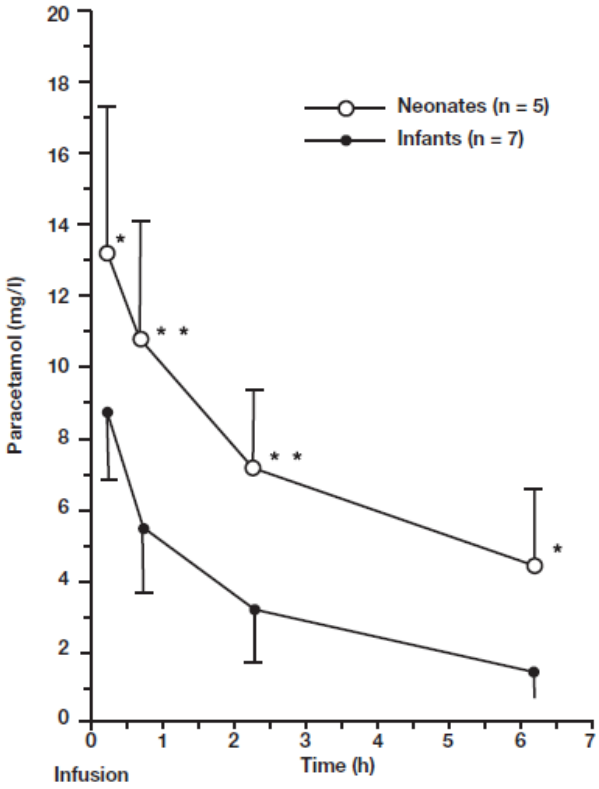
The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Special Populations

Neonates and Infants <6 months of age

Clinical Trials examining the pharmacokinetics of paracetamol solution for infusion in neonates and infants <6 months of age are limited. The safety and efficacy of paracetamol solution for infusion 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:

[Figure 2]



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

[Table 8] Pharmacokinetic parameters of all children and of children aged less than and over 10 days

	Total	**<10 days**	**>10 days**	**P**
$T_{1/2}$, 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 the plasma; V = volume of distribution.				

The infants in the study were aged between 1 and 232 days; mean 88 ± 95 days. In the neonates aged less than 10 days, the gestational age was 37.4 ± 3.9 weeks (32 to 41.3 weeks). The weight of the neonates at the time of the study was 2.578 ± 0.959 kg (1 to 3.8); birth weight was 2.578 ± 1.022 kg (1 to 3.920 kg). The mean administered dose was 15.3 ± 2 mg/kg (13.40 to 20 mg/kg).

In neonates, the plasma half-life is longer than in infants 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.

Elderly (>65 years)

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

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 Dose and method of administration).

Hepatic Impairment

Paracetamol should be administered with caution to patients with hepatic impairment (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use). Hepatic impairment may decrease the clearance of paracetamol or increase the probability of hepatic toxicity.

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 (approximately 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/m^2/day, similar to human exposure) and male rats (up to 1800 mg/m^2/day, 0.7 times human exposure). Equivocal evidence of carcinogenic potential (mononuclear cell leukaemia) was observed only in female rats at 1900 mg/m^2/day, or 0.7 times the maximum anticipated clinical exposure on a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose,

Acetic acid,

Sodium acetate trihydrate,

Sodium citrate,

Sodium hydroxide,

Hydrochloric acid,

Water for injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate. Protect from light.

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).

6.5 Nature and contents of container

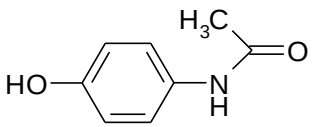
PARACETAMOL IV PFIZER is available in 50 mL and 100 mL (10 mg/mL) hermetically sealed PVC bags, contained within a metallised triple layer, double lamina outer packaging. They are available, in pack sizes of 12s.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Structure



Chemical name: 4-acetamidophenol

Molecular weight: 151.2

CAS Number

103-90-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

15 January 2013

10. DATE OF REVISION

12 February 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Labeling update regarding premature constriction/closure of the fetal ductus arteriosus.
4.3, 4.8, 5.1 and 5.3	Minor editorial changes.

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