PRODUCT INFORMATION

PERFALGAN
(paracetamol)

SOLUTION FOR INFUSION

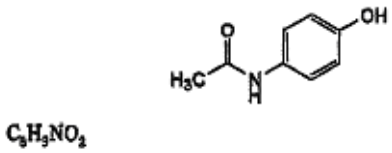
NAME OF THE MEDICINE

Australian Approved Name

Paracetamol.

Chemical Structure

Paracetamol is 4 – acetamidophenol. The structural formula is:



$C_8H_9NO_2$

Molecular weight: 151.2
CAS registry number: 103-90-2

DESCRIPTION

PERFALGAN (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. 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.

PERFALGAN solution for infusion contains 10mg/mL of paracetamol (50mL vial contains 500 mg of paracetamol, 100mL vial contains 1 g of paracetamol)

PERFALGAN solution for infusion contains mannitol, cysteine hydrochloride, sodium phosphate – dibasic 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.

PERFALGAN 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.

PERFALGAN 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.

PHARMACOKINETICS

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 PERFALGAN 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 (Cmax) of paracetamol observed following intravenous infusion of 1 g PERFALGAN 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 PERFALGAN 10 mg/mL, solution for infusion is similar to that observed following infusion of 1g propacetamol (containing 500mg paracetamol). The maximum plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg of PERFALGAN 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

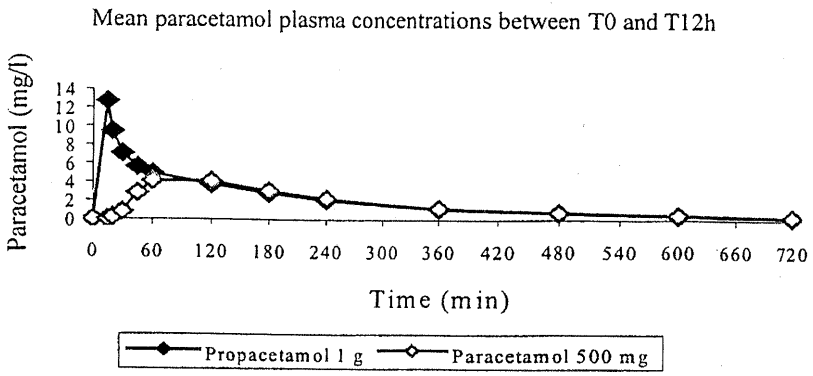


Table 1

Pharmacokinetic parameters of paracetamol (mean ± sd)

	Propacetamol 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 2g propacetamol, (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:

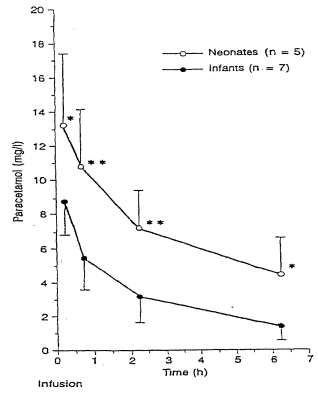
The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Neonates and Infants <6 months of age

Clinical Trials examining the pharmacokinetics of PERFALGAN in neonates and infants <6 months of age are limited. The safety and efficacy of PERFALGAN 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 PERFALGAN 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 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 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 20mg/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 DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Paracetamol should be administered with caution to patients with hepatic impairment (see CONTRAINDICATIONS and PRECAUTIONS). 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, PERFALGAN and Propacetamol. Propacetamol 2g is equivalent to PERFALGAN 1g. Refer to DOSAGE and ADMINISTRATION for the correct dosing instructions for PERFALGAN.

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 PERFALGAN 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 PERFALGAN 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 PERFALGAN 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
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 3b

Overview of repeated-dose efficacy criteria – ITT population

	Inj APAP 1g	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 (TO-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	-20.2	33.1	0.0004
SD	94.6	95.4	
Composite endpoint MPAI (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 PERFALGAN 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 PERFALGAN 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 PERFALGAN 1g versus placebo after repeated doses.

An overview of the results are shown in Table 4

Table 4

	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

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 PERFALGAN 15mg/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 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 6

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 PERFALGAN which delivers 1g of paracetamol for every 2g of propacetamol administered.

<u>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</u>

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 15mg/kg PERFALGAN) 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 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 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.

INDICATIONS

PERFALGAN 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

PERFALGAN 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 ADMINISTRATION).

PRECAUTIONS

PERFALGAN should be used with caution in cases of:

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

(see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS)

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 PERFALGAN. If the daily dose of paracetamol from all sources exceeds the maximum, severe hepatic injury may occur (See OVERDOSAGE)

Hepatic Injury

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

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

Pregnancy Category (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 foetus having been observed.

The reproductive toxicity of IV PERFALGAN 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

Nevertheless, PERFALGAN 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. PERFALGAN 10 mg/mL, solution for infusion may be used in breast-feeding women, but caution should be observed.

Genotoxicity

Paracetamol was not mutagenic in the bacterial mutagenicity assay, but it was clastogenic in mammalian cell assay systems *in vitro* (mouse TK, human lymphocyte) and in a mouse micronucleus assay *in vivo.* The clastogenic effect was dose-dependent, and the mechanism appears to involve inhibition of replicative DNA synthesis and ribonucleotide reductase at above threshold doses. The clinical significance of clastogenic findings is equivocal as positive findings *in vivo* only occurred at exposures *(ca.* 8 times the maximum anticipated clinical exposure, based on 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/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.

INTERACTIONS WITH OTHER MEDICINES

Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

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.

ADVERSE EFFECTS

The overall incidence of adverse events in Perfalgan-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)

	Perfalgan % 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		
Diarrhea	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		
Anemia	2.7	6.9
Post operative hemorrhage	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/Metabolic		
Hyperglycemia	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)

	Perfalgan % n = 95
Skin and Appendage Injection site pain Injection site reaction	14.74
Neurological Hypotonia	1.05
Gastrointestinal Nausea Vomiting Abdominal pain Eructation	1.05 5.26
Body As A Whole Fever	1.05

As with all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ System	Rare >1/10000, <1/1000	Very rare <1/10000	Isolated reports
General	Malaise	Hypersensitivity reaction	
Cardiovascular	Hypotension	Shock	
Liver	Increased levels 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

DOSAGE AND ADMINISTRATION

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

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

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

Intravenous route:

PERFALGAN 10 mg/mL, solution for infusion should not be mixed with other medicinal products.

Use of the 100 mL 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 PERFALGAN in neonates and infants <6 months of age (See PHARMACOKINETICS)

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 per 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.

Perfalgan 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 Perfalgan 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.

Paediatric Patients

PERFALGAN 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 PERFALGAN (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 PERFALGAN 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).

OVERDOSAGE

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 PERFALGAN overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

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 PERFALGAN.
- 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 AND STORAGE CONDITIONS

Paracetamol 10 mg/mL solution for infusion is available in 50 mL and 100mL clear glass vials in a pack size of 12 vials.
One 50 mL vial contains 500 mg paracetamol and 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.
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).

NAME AND ADDRESS OF SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
556 Princes Highway
NOBLE PARK VIC 3174

POISON SCHEDULE OF MEDICINE
Schedule 4 (Prescription Medicine).

DATE OF FIRST INCLUSION ON THE ARTG: 19 October 2004
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