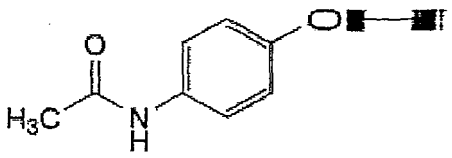
Paracetamol Actavis

PRODUCT INFORMATION

Name of the medicine

Paracetamol. The chemical name for paracetamol is 4-acetamidophenol. Its structural formula is:



$C_8H_9NO_2$ Molecular weight: 151.2 CAS No.: 103-90-2

Description

Paracetamol is a white, crystalline solid powder which is odourless or almost odourless and hygroscopic. 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 hydoxides.

Paracetamol Actavis solution for infusion is a clear solution that contains 1000 mg/100 mL of paracetamol. The solution also contains mannitol, cysteine hydrochloride monohydrate, dibasic dihydrate sodium phosphate, sodium hydroxide, hydrochloric acid, water for injections.

Pharmacology

Pharmacodynamics

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

Paracetamol 1000 mg/100 mL solution for infusion provides onset of pain relief within five to ten minutes after the start of administration. The peak analgesic effect is obtained in one hour and the duration of this effect is usually four to six hours.

Paracetamol 1000 mg/100 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 of paracetamol 1000 mg/100 mL is similar to that observed following infusion of propacetamol 2 g (containing paracetamol 1 g). 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 paracetamol 1000 mg/100 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 paracetamol 500 mg/50 mL solution for infusion is similar to that observed following infusion of propacetamol 1 g. The maximum plasma concentration (C_{max}) of paracetamol observed at the end of 15 minutes intravenous infusion of paracetamol 500 mg/50 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, two 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. See Figure 1 and Table 1 below.

Figure 1

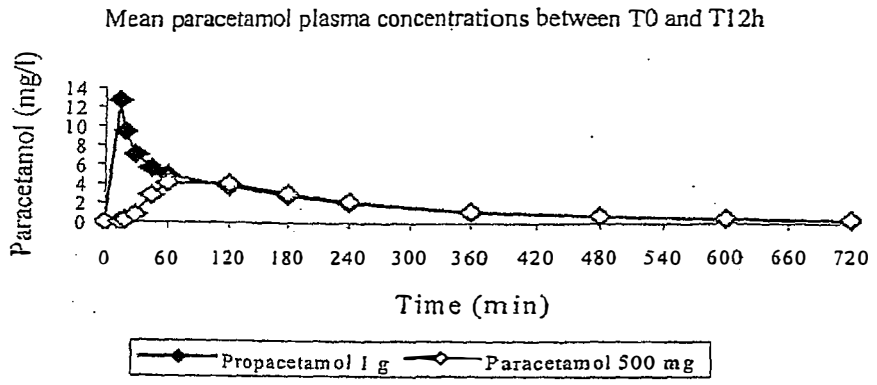


Table 1: Pharmacokinetic parameters of paracetamol (mean ±sd)

	Propacetamol 1 g - i.v. (n=12)	Paracetamol 500 mg - oral (n=12)	p value
C_{max} (µg/mL)	12.72 ± 3.51	5.49 ± 1.89	p < 0.0001
T_{max} (h)	0.25	1.46 ± 0.57	p < 0.0001
t½ (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 the infusion.

Distribution

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

Paracetamol is not extensively bound to plasma proteins.

Following infusion of proparacetamol 2 g, (equivalent to paracetamol 1 g) 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 sulfuric 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 paracetamol 1,500 mg/L, 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 to 80%) and sulfate (20 to 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 paracetamol in neonates and infants < 6 months of age are limited. The safety and efficacy of paracetamol in premature neonates has not been established. In a trial of 12 children between 1 and 232 days of age, which included five children less than 10 days of age the pharmacokinetic results for paracetamol are as follows:

Figure 2: Paracetamol concentrations (mean ± SD) versus time after a 15 minute propacetamol infusion. * p<0.05, ** p<0.01, differences between groups

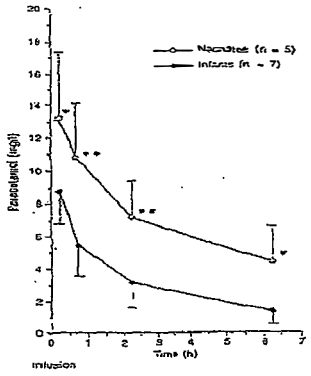


Table 2: Pharmacokinetic parameters of all children aged less than and over 10 days

	Total	< 10 days	> 10 days	p value
t½ (h)	2.7 (1.0)	3.5 (0.5)	2.1 (0.9)	p < 0.05
AUC, µg/L/h	41.3 (25.9)	64.0 (23.7)	25.0 (10.9)	p < 0.01
CL (l/h/kg)	0.275 (0.2)	0.149 (0.067)	0.365 (0.219)	p < 0.05
Vd(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; Vd = 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 kg); birthweight 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 sulfate 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 hours) 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 sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. It is recommended that there be an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance ≤30 mL/min) (see **Dosage and Administration**).

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

Elderly
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 itself and propacetamol. Propacetamol 2 g is equivalent to paracetamol 1 g. See **Dosage and Administration** for the correct dosing instructions for Paracetamol Actavis.

Analgesia - Adults
Two phase III studies were conducted to compare the safety and analgesic efficacy of intravenous (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 intravenous paracetamol for the treatment of postoperative pain following orthopaedic surgery

151 patients were included in this study; 49 patients were administered paracetamol 1 g and 52 patients placebo. The groups of patients were comparable with regard to demographic and baseline characteristics. 137 (90.7%) of patients received four administrations over 24 hours, two (1.3%) patients received three; two (1.3%) patients received two and ten (6.6%) patients received only one administration.

The primary measured efficacy endpoint parameter of the trial was the evaluation of paracetamol 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 (patient controlled analgesia) morphine); patients global evaluation (PGA). The secondary measured efficacy endpoint parameter was paracetamol 1 g versus placebo after repeated doses.

An overview of the results is shown in Tables 3a and b.

Table 3a: Overview of analgesic efficacy criteria - Single dose evaluation - ITT population

	Paracetamol IV (n=50)	Placebo (n=52)	p Value Paracetamol/Placebo
TOTPAR			
Mean	6.6	2.2	0.0001
SD	5.9	3.8	
SPID			
Mean	2.3	-0.6	0.0001
SD	3.6	3.5	
SPAID			
Mean	104.7	-27.7	0.0001
SD	112.9	92.4	
SPRID			
Mean	9.0	1.6	0.0001
SD	8.7	6.2	
MAXPR			
Mean	2.0	0.9	0.0001
SD	1.4	1.1	
MAXPID			
Mean	1.0	0.4	0.0001
SD	0.8	0.8	
MAXPAID			
Mean	36.6	11.9	0.0001
SD	23.4	20.0	
MAXPRID			
Mean	3.0	1.3	0.0001
SD	2.1	1.8	
Median time to rescue medication (hr) [95% confidence interval]	3.0 [1.4;4.0]	0.8 [0.6;1.1]	0.0001

Table 3b: Overview of repeated dose efficacy criteria - ITT population

	Paracetamol IV 1 g	Placebo	p Value Paracetamol/Placebo
Quantity of rescue medication (mg of equivalent morphine dose) over 24 h			
N	48	52	
Mean	38.33	57.41	0.0007
SD	35.14	52.3	
Number of requested administrations of rescue medication over 24 h			
N	48	51	
Mean	47.4	89.3	0.0003
SD	39.1	94.5	
Actual number of requested administrations of rescue medication over 24 h			
N	48	52	
Mean	27.8	42.3	0.0001
SD	20.2	26.0	
MPI (T0-T24h)			
N	46	47	
Mean	1.4	1.6	0.0202
SD	0.5	0.6	

	Paracetamol IV 1 g	Placebo	p Value Paracetamol/Placebo
MPAI (T0-T24h)			
N	46	47	
Mean	31.6	39.6	0.0006
SD	17.0	18.5	
Composite endpoint MPI (T0-T24h)			
N	45	47	
Mean	-20.2	33.1	0.0004
SD	94.6	95.4	
Composite endpoint MPAI (T0-T24h)			
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 24 h)			
N	49	52	
Mean	81.6	61.8	0.0019
SD	42.8	37.3	

Efficacy of intravenous paracetamol for the treatment of postoperative pain following oral (postdental) surgery

152 patients were included in this study; 51 patients were administered paracetamol 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 1 g paracetamol 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 1 g versus placebo after repeated doses.

An overview of the results is shown in Table 4.

Table 4

	Paracetamol IV (n=51)	Placebo (n=50)	p Value Paracetamol/Placebo
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	

	Paracetamol IV (n=51)	Placebo (n=50)	p Value Paracetamol/Placebo
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% confidence interval]	 0.25 Not estimable	 0.25 Not estimable	0.5557
t-MAXPID Median [95% confidence interval]	 0.25 Not estimable	 0.25 Not estimable	0.7167
t-MAXPAID Median [95% confidence interval]	 0.5 [0.25;0.5]	 0.25 Not estimable	0.283
t-MAXPRID Median [95% confidence interval]	 0.25 Not estimable	 0.25 Not estimable	0.5557
Median time to onset (min) [95% confidence interval]	 8.0 [5.0;12.0]	 Not estimable	0.0001
Median time to rescue medication (hr) [95% confidence interval]	 2.1 [1.4;3.4]	 0.7 [0.5;0.8]	0.0001

Analgesia- Children

Efficacy of intravenous paracetamol with postoperative pain (hernia repair)

183 patients were included in this study, of which 95 patients were administered paracetamol 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, one, two, three, four, five and six hours postdose. 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 less than or equal to 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 is 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 hr	T 2 hr	T 3 hr	T 4 hr	T 5 hr	T 6 hr
Patient Number	95	95	95	95	95	95	95	95
Paracetamol IV	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 + centre + TRT; BLPI = baseline pain intensity (VAS-investigator); TRT = treatment

VAS (Child) - ITT Population

Treatment	T 15 min	T 30 min	T 1 hr	T 2 hr	T 3 hr	T 4 hr	T 5 hr	T 6 hr
Patient Number	45	45	45	45	45	45	45	45
Paracetamol IV	20.8	31.7	34.4	36.4	38.8	39.1	39.1	39.6
SD	27.9	29.2	26	35.5	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 + centre + TRT; BLPI = baseline pain intensity (VAS-investigator); TRT = treatment

OPS - ITT Population

Treatment	T 15 min	T 30 min	T 1 hr	T 2 hr	T 3 hr	T 4 hr	T 5 hr	T 6 hr
Patient Number	95	95	95	95	95	95	95	95
Paracetamol IV	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 + centre + TRT; BLPI = baseline pain intensity (VAS-investigator); TRT = treatment

ITT Population

Treatment	T 15 min	T 30 min	T 1 hr	T 2 hr	T 3 hr	T 4 hr	T 5 hr	T 6 hr
Patient Number	95	95	95	95	95	95	95	95
Paracetamol IV	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) PID = BLPI + centre + TRT; BLPI = baseline pain intensity (VAS-investigator); TRT = treatment

Table 6: Measure of analgesic efficacy: AUC over 6 hours (mean score ± SD) - ITT population

		Treatment group (n=95)	
	Statistics	Paracetamol IV	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*

* Analyses of covariance

Antipyrexia

Propacetamol is the prodrug of paracetamol; it delivers paracetamol 1 g for every propacetamol 2 g administered.

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

41 children with acute fever (ear temperature between 38.5 and 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 propacetamol 30 mg/kg (equivalent to paracetamol 15 mg/kg) in comparison with placebo in children with acute fever of infectious origin (changes in body temperature (BT) from 0.5 to 6 hours postdose).

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 body temperature 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 remedication (with calculation of time at which 50% of children require remedication) over the TO-T6 period, number and percentage of children requiring rescue medication over the TO-T6 period; safety: vital signs and adverse events.

An overview of the results is shown in Tables 7 and 8.

Table 7: Primary criterion: mean body temperature change from baseline of 6 hr

Treatment	T 30 min	T 1 hr	T 2 hr	T 3 hr	T 4 hr	T 5 hr	T 6 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=BL Bodytemp+centre=trt;							
(c) Response=BL Bodytemp+centre+trt+(trt*centre)+(trt*BL Bodytemp							

Table 8: Overview of secondary efficacy criteria

	Propacetamol (n=20)	Placebo (n=21)	p-Value
Time to first remedication over 6 hr (hr)(median)	Not established	5.0	0.0046
No patients receiving ≥ 1 rescue med. n(%)	2 (10%)	11 (52.4%)	0.004
Time to reach BT < 38°C over 6 hr (hr)(median)	2.0	Not established	0.0001
No patients reaching at least BT< 38°C over 6 hr n(%)	18 (90%)	5 (23.8%)	0.001
Max BT - change from baseline over 6 hrs (°C)	2.0 ± 0.7	0.6 ± 0.6	0.0001
T-max BT - change over 6 hr (hr)(median)	3.0	2.0	0.0316
Weighted sum of BT - changes over 6 hr (°C.hr)	7.9 ± 3.8	-0.1 ± 3.6	0.0001
Weighted sum of BT - changes over 4 hr (°C.hr)	5.2 ± 2.0	0.2 ± 2.2	0.0001
Weighted sum of % of BT - reduction over 6 hr (%.hr)	390 ± 170	-20 ± 190	0.0001
Weighted sum of % of BT - reduction over 4 hr (%.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	-100 ± 40	0.0003

Indications

Relief of mild to moderate pain and reduction of fever where an intravenous route of administration is considered clinically necessary.

Contraindications

Paracetamol Actavis is contraindicated with:

- hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients
- severe hepatocellular insufficiency

- 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 four to six days. Treatment with antidote should be given as soon as possible (see **Dosage and Administration**).

Precautions

Paracetamol Actavis should be used with caution in cases of:

- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance less than or equal to 30 mL/minute) (see **Dosage and Administration** and **Pharmacokinetics**),
- -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.

The total dose of paracetamol should not exceed 4 g/day. It is important to consider the contribution of all paracetamol containing medications, including non-prescription, oral or PR (per rectum) forms of the drug to this total daily paracetamol dose prior to administering Paracetamol Actavis. 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 Paracetamol Actavis.

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 foetus having been observed.

The reproductive toxicity of intravenous (IV) paracetamol has not been directly tested in animal studies. IV administration of maternotoxic doses of the prodrug, 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 sevenfold (rats; AUC basis) the maximum anticipated clinical exposure to paracetamol. The clinical significance of these findings is not known. No signs of prenatal/postnatal toxicity were observed in rats treated with IV propacetamol at maternal exposures (based on AUC) greater than threefold those anticipated at the maximum clinical dose.

Use in lactation
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on breastfeeding 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 1000 mg/100 mL solution for infusion may be used in breastfeeding women.

Carcinogenicity
No evidence of carcinogenic potential was observed for paracetamol in long-term oral studies in mice (up to 3,000 mg/m^2/day, similar to human exposure) and male rats (up to 1,800 mg/m^2/day, 0.7 times human exposure). Equivocal evidence of carcinogenic potential (mononuclear cell leukaemia) was observed only in female rats at 1,900 mg/m^2/day, or 0.7 times the maximum anticipated clinical exposure on a mg/m^2 basis.

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 eight times the maximum anticipated clinical exposure, based on C_{max}) greater than that for hepatotoxicity, and at doses that were associated with significant cytotoxicity.

Interactions with other medicines

Probenecid causes an almost twofold 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 paracetamol treated patients compared to placebo within the clinical trial set can be observed in Tables 9 - 11 below.

Table 9: Adverse events in Adults - greater than 1% (observed in the clinical trial set)

	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	
Pruritis	3.3	4.9
Respiratory		
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	

Table 10: Adverse events in Children - greater than 1% (observed in the clinical trial set)

	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

Postmarketing adverse events for propacetamol/paracetamol

As with all paracetamol products, adverse drug reactions are rare (> 1/10,000, < 1/1,000) or very rare (< 1/10,000), they are described below:

Table 11

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

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

Isolated reports of thrombocytopenia have been observed.

Dosage and Administration

Intravenous route
Paracetamol Actavis 1000 mg/100 mL solution for infusion should not be mixed with other medicinal products.

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

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

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

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

Neonates, infants and children weighing up to 33 kg (about 11 years old)
Paracetamol 15 mg/kg per administration, i.e. 1.5 mL of solution per kg, up to four times a day. The minimum interval between each administration must be 6 hours. The maximum daily dose must not exceed 60 mg/kg.

Term newborn infants, infants, toddlers and children weighing less than 10 kg (up to approximately 1 year old): it is recommended to reduce the dosage by half, i.e. 7.5 mg/kg paracetamol per administration, without exceeding 4 administrations per day.

The safety and efficacy of paracetamol in premature neonates has not been established. There are limited data on the use of paracetamol in neonates and infants < 6 months of age (See **Pharmacokinetics**).

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

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

Paracetamol Actavis 1000 mg/100 mL solution for infusion can also be diluted in a 0.9% sodium chloride or 5% glucose solution up to one tenth. In this case, use the diluted solution within the hour following its preparation (infusion time included).

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

It is recommended that for the administration of Paracetamol Actavis 1000 mg/100 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.

Overdosage

Contact the Poisons Information Centre (telephone: 13 11 26) for advice on the management of an 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; paracetamol 7.5 g or more in a single administration in adults or 140 mg/kg of bodyweight 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 four to six 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 parenteral 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 Actavis 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 ten 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 intravenous paracetamol.
- 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 Actavis	Paracetamol 1000 mg/100 mL; Solution for infusion (clear solution), 100 mL clear glass vials: Pack sizes of 1'*,10* and 12 vials.

Store below 25°C. Store vials in the original carton to protect from light. Do not refrigerate or freeze.

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

For single use in one patient only. The product should be used immediately after opening and any unused solution should be discarded.

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

*not marketed

Name and address of the sponsor

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Upper Ground Floor
183 Melbourne Street
North Adelaide SA 5006
Australia

ABN 42 122 896 468
Phone Number:1300 881 893

Poison schedule of the medicine

PRECRIPTION ONLY MEDICINES - S4

Date of approval

Approved by the Therapeutic Goods Administration on XX XXX XXXX.
PARACETAMOL ACTAVIS/PI/052011/1