1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ASPEN PARACETAMOL 1 g IV solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml vial of ASPEN PARACETAMOL 1 g IV contains 1 g paracetamol.

Preservative: Cysteine hydrochloride monohydrate 0,025 % w/v

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

ASPEN PARACETAMOL 1g IV solution for infusion is clear and slightly yellowish.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ASPEN PARACETAMOL 1g IV is indicated for:

The short-term treatment (not exceeding 24 hours) of mild to moderate pain, e.g. after dental procedures and minor orthopaedic procedures, and the short-term treatment of fever, when the oral route is unsuitable.

4.2. Posology and method of administration

Posology

Adults

The recommended dose in patients weighing more than 50 kg:

ASPEN PARACETAMOL 1g IV per administration, i.e. one 100 ml vial, up to four times a day. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 4 g.

The recommended dose in patients weighing less than 50 kg but weighing more than 33 kg:

ASPEN PARACETAMOL 1g IV: 15 mg/kg per administration, i.e. 1,5 ml solution per kg up to 4 times a day. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 60 mg/kg without exceeding a maximum daily dose of 3 g.

DO NOT EXCEED THE RECOMMENDED DOSE

Dosing recommendations are presented in the table below:

Patient weight (non-oedematous weight)	**Paracetamol dose (10 mg/mL) per administration**	**Minimum interval between each administration**	**Maximum daily dose***
> 50 kg	1 g (i.e. 100 mL vial up to 4 times a day	4 hours	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 a day	4 hours	≤ 60 mg/kg Must not exceed 3 g in 24 hours

***** The maximum daily dose takes into account all the medicines containing paracetamol.

The dosage should be calculated on non-oedematous weight.

Special populations

Severe renal insufficiency

It is recommended to leave a minimum interval of 6 hours between each administration in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see section 5.2).

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 3 g/day.

Paediatric population

The safety and efficacy of ASPEN PARACETAMOL 1 g IV in children weighing less than 33 kg (approximately 11 years old) has not been established (see section 4.3)**.**

Method of administration

For intravenous administration.

ASPEN PARACETAMOL 1g IV is to be administered as a 15-minute intravenous infusion.

Before administration, the product should be visually inspected for any particulate matter and discolouration. It is intended for single-use only. Once opened, the vial should be used immediately.

Any unused solution should be discarded.

Careful monitoring to avoid air embolism is needed, notably at the end of the infusion, especially if a central venous catheter is used for the infusion.

ASPEN PARACETAMOL 1g IV should not be mixed with other medicinal products.

4.3. Contraindications

ASPEN PARACETAMOL 1 g IV is contraindicated in:

- Patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol), or to any of the excipients (see section 6.1).
- Severe hepatocellular insufficiency or active liver disease including alcoholic hepatitis.
- Children weighing less than 33 kg (approximately 11 years old) as safety and efficacy have not been established (see section 4.2).

4.4. Special warnings and precautions for use

It is recommended to use a suitable oral analgesic treatment as soon as this administration route is possible.

ASPEN PARACETAMOL 1G IV contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose, and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

In order to avoid the risk of overdose, check that other medicines administered do not contain paracetamol.

Doses of ASPEN PARACETAMOL 1g IV in excess of those recommended may cause severe liver damage.

Clinical symptoms and signs of liver damage are usually seen first after two days, with a maximum occurring usually after 4 – 6 days. Treatment with antidote should be given as soon as possible (see section 4.9)

Patients recovering from any form of liver disease should not be given excessive quantities of ASPEN PARACETAMOL 1g IV.

ASPEN PARACETAMOL 1g IV should be used with caution in patients with mild to moderate liver impairment and is contraindicated where there is active disease, particularly alcoholic hepatitis.

ASPEN PARACETAMOL 1g IV should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia).
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency which may lead to haemolytic anaemia.
- Severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see section 4.2 and 5.2).
- Chronic alcoholism, excessive alcohol intake.
- Chronic malnutrition, anorexia, bulimia, cachexia (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia.

Renal disease

ASPEN PARACETAMOL 1 g IV should be used with caution in patients suffering from renal disease, as prolonged excessive use of paracetamol can produce nephropathy. Paracetamol induced renal function impairment may be sufficiently severe and could result in uraemia, especially with prolonged use of high doses. In patients with renal impairment with a creatinine clearance of 30 mL/minute or less the elimination of paracetamol is delayed, therefore a 6 hourly dose interval is recommended (see section 4.2).

Severe cutaneous adverse reactions (SCARs)

Severe Cutaneous Adverse Reactions (SCARS) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with ASPEN PARACETAMOL 1 g IV must immediately be discontinued and appropriate treatment instituted.

Salicylates

Salicylates in prolonged treatments together with ASPEN PARACETAMOL 1 g IV significantly increased the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal diseases, and cancer of the urinary bladder. Do not exceed the recommended individual dosages for salicylates and ASPEN PARACETAMOL 1 g IV (see section 4.5).

Anticoagulants

The anticoagulant effect could be increased when high doses of ASPEN PARACETAMOL 1 g IV are used together with anticoagulants, such as warfarin (see section 4.5).

Hepatotoxic medicines

The risk of ASPEN PARACETAMOL 1 g IV toxicity may be increased in patients receiving potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes (see section 4.5).

4.5. Interaction with other medicines and other forms of interaction

Probenecid

Probenecid causes an almost 2-fold reduction in clearance of ASPEN PARACETAMOL 1g IV by inhibiting its conjugation with glucuronic acid a reduction of ASPEN PARACETAMOL 1g IV dose should be considered when administered concomitantly with probenecid.

Salicylamide

Salicylamide may prolong the elimination half-life of ASPEN PARACETAMOL 1g IV. Salicylates in prolonged treatments together with paracetamol significantly increased the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal diseases, and cancer of the urinary bladder. The recommended individual doses for ASPEN PARACETAMOL 1g IV. and the salicylates should not be exceeded.

Enzyme inducers

Caution should be paid to the concomitant intake of ASPEN PARACETAMOL 1g IV and enzyme-inducing substances as these substances increase the risk of paracetamol induced liver injury. These substances include, but are not limited to barbiturates,

rifampicin, isoniazid, carbamazepine, anticoagulants, zidovudine, chronic use of alcohol, amoxicillin, clavulanic acid or hepatotoxic medicines.

Medicines that induce liver microsomal enzymes such as barbiturates or primidone could decrease the therapeutic effect of ASPEN PARACETAMOL 1g IV.

Phenytoin

Phenytoin administered concomitantly with ASPEN PARACETAMOL 1g IV may result in decreased paracetamol efficacy and an increased risk of hepatotoxicity. Patients receiving phenytoin should avoid large and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatoxicity.

Metoclopramide

The absorption of ASPEN PARACETAMOL 1g IV may be accelerated when used together with metoclopramide.

Flucloxacillin

Caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with a risk factor for glutathione deficiency such as severe renal impairment, sepsis, malnutrition and chronic alcoholism. Close monitoring is recommended in order to detect the appearance of acid base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

Anticoagulants

The anticoagulant effects may increase when high doses of ASPEN PARACETAMOL 1g IV are used together with anticoagulants, coumarin (e.g. warfarin) and/or indandione derivates.

Increased monitoring of INR values should be conducted during the period of concomitant use, as well as 1 week after discontinuation of ASPEN PARACETAMOL 1g IV.

4.6. Fertility, pregnancy and lactation

Pregnancy

Clinical experience of intravenous administration of ASPEN PARACETAMOL 1g IV is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus/newborn infant.

Prospective data on pregnancies exposed to overdose did not show an increase in malformation risk.

ASPEN PARACETAMOL 1g IV should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended dosage and duration must be strictly observed.

Breastfeeding

After oral administration, paracetamol is excreted into breast milk in small quantities.

Rash in nursing infants has been reported. Caution is advised when administering ASPEN PARACETAMOL 1g IV to women who are breastfeeding their infants.

Fertility

No data.

4.7. Effects on ability to drive and use machines

ASPEN PARACETAMOL 1g IV has no influence on the ability to drive or operate machinery.

However, ASPEN PARACETAMOL 1g IV will be administered in hospital whilst the patient is under the supervision of a healthcare professional.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Thrombocytopenia, agranulocytosis, leucopenia, pancytopenia, neutropenia, anaemia.	
Immune system disorders		Hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock, angioedema.	
Vascular disorders		Hypotension, flushing.	
Gastrointestinal disorders			Pancreatitis, nausea, vomiting.
Hepatobiliary disorders		Increased levels of hepatic transaminases, hepatitis.	Hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders			Dermatitis, erythema, pruritus, rash, urticaria.
Renal and urinary disorders		Renal colic, renal failure and sterile pyuria.	
General disorders and administrative site conditions		Malaise.	

Post-marketing experience

System organ class	Frequency unknown (cannot be estimated from the available data)
Cardiac disorders	Tachycardia
Hepatobiliary disorders	Fulminant hepatitis
Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4).
General disorders and administrative site conditions	Administration site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to **SAHPRA** via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Prompt treatment is essential.

In the event of an overdosage consult a doctor immediately or take the person to a hospital directly. A delay in starting treatment may mean that antidote is given too late to

be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to ASPEN PARACETAMOL 1g IV toxicity is increased in patients who have taken repeated high doses (greater than 5-10 g/day) of paracetamol for several days.

There is a risk of overdosage, particularly in elderly subjects, in young children, in cases of chronic alcoholism, in patients with chronic malnutrition, AIDS and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain. Mild symptoms during the first two days of acute overdosage do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours or later after administration, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time/increased INR. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

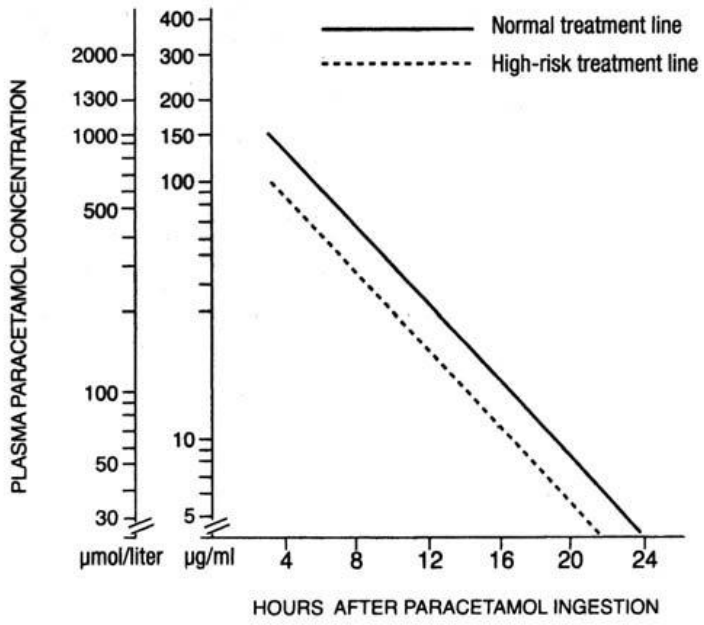
Treatment

- Immediate hospitalisation.
- Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.
- N-acetylcysteine (NAC) should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage; although treatment up to 36 hours after ingestion may still be of benefit especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml

dextrose 5 % w/v injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose 5 % w/v injection over the next four hours and then 100 mg/kg in 1000 ml dextrose 5 % w/v injection over the next sixteen hours.

Sodium chloride 0,9 % w/v may be used where glucose 5 % w.v is unsuitable.

The volume of intravenous fluid should be modified for children. Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.



Paracetamol overdose with IV Infusions

After an overdosage with an intravenous infusion, the standard nomogram used for determining treatment from paracetamol plasma concentrations following oral ingestion of an overdose of paracetamol, may not be appropriate. Paracetamol plasma concentrations more than 4 hours after intravenous injection may be lower than those predicted for the same oral dose at the same time point after ingestion.

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly

until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line” (refer to paracetamol nomogram above).

Prothrombin index correlates best with survival. Monitor all patients with significant overdose forat least ninety six hours.

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.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

Pharmacotherapeutic group: Other analgesics and antipyretics.

ATC code: N02BE01.

Mechanism of action

Paracetamol has analgesic and antipyretic activities.

The precise mechanism of the analgesic and antipyretic properties of paracetamol has not been established; it may involve central and peripheral actions.

5.2. Pharmacokinetic properties

Absorption

In adults, paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 1 g of paracetamol in adults is about 30 µg/ml.

Distribution

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

Paracetamol is not extensively bound to plasma proteins.

Following infusion of 1 g paracetamol in adults, significant concentrations of paracetamol (about 1,5 µg/ml) were observed in the cerebrospinal fluid as and from the 20th minute following infusion.

Biotransformation

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 benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid.

Elimination

The metabolites of paracetamol are mainly excreted in the urine. Ninety percent (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 elimination half-life is 2,7 hours and body clearance is 18 litres/hr.

Paediatric population

The pharmacokinetic parameters of paracetamol observed in children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1,5 to 2 hr) than in adults. Total excretion of paracetamol and its metabolites is the same at all ages.

Special populations

Renal insufficiency

In cases of severe renal impairment (creatinine clearance < 30 ml/min), the elimination of paracetamol is 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.

Therefore, it is recommended to leave an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see section 4.2).

Elderly population

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cysteine chlorhydrate monohydrate, disodium phosphate dihydrate, hydrochloric acid (for pH adjustment), mannitol, sodium hydroxide (for pH adjustment) and water for injection.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C.

Do not refrigerate or freeze.

Keep the vial(s) in the outer carton in order to protect from light.

Once opened, the vial should be used immediately.

Any unused portion should be discarded.

6.5. Nature and contents of container

ASPEN PARACETAMOL 1g IV is available in 100 ml clear glass vials, [closed with bromobutyl stoppers and sealed with aluminium caps], in pack sizes of 1 vial and 10 vials, respectively.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

45/2.7/0374

9. DATE OF FIRST AUTHORISATION

19 April 2013

10. DATE OF REVISION OF TEXT

22 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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