PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

PERFALGAN 1 g Solution for Infusion

COMPOSITION:

PERFALGAN 1 g:

Each 100 ml vial contains 1 g paracetamol as active ingredient.

Preservative: Cysteine hydrochloride monohydrate 0,025 % m/v.

Excipients: Mannitol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid, water for injection and nitrogen.

PHARMACOLOGICAL CLASSIFICATION:

A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

PHARMACOLOGICAL ACTION:

Paracetamol has analgesic and antipyretic activities.

Pharmacodynamic properties

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

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 l/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.

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 reaction 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. However, during massive poisoning, the quantity of this toxic metabolite is increased.

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 elimination half-life is 2,7 hours and total body clearance is 18 l/h.

Children:

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 h) 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 DOSAGE AND DIRECTIONS FOR USE).

Hepatic impairment:

Paracetamol should be used with caution in patients with mild to moderate liver impairment and is contraindicated when there is active disease, particularly alcoholic hepatitis because of CYP 2E1 induction, which leads to increased formation of the hepatotoxic metabolite of paracetamol. (See CONTRAINDICATIONS).

Elderly subjects:

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

INDICATIONS:

PERFALGAN 1 g is indicated for:

- the short-term treatment 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.

CONTRAINDICATIONS:

PERFALGAN 1 g is contraindicated in:

- cases of hypersensitivity to paracetamol or to paracetamol hydrochloride (pro-drug of paracetamol) or to any of the excipients.
- Cases of severe hepatocellular insufficiency or decompensated active liver disease including alcoholic hepatitis.

WARNINGS AND SPECIAL PRECAUTIONS:

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

In order to avoid the risk of overdose, check that other medicines administered (including prescription and non-prescription medicines) do not contain paracetamol.

Doses of PERFALGAN 1 g in excess of those recommended may cause very severe liver damage. Clinical symptoms and signs of liver damage are usually seen first after two days of paracetamol overdose. Maximum liver damage symptoms are usually observed after 4 to 6 days. Treatment with antidote should be given as soon as possible (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

PERFALGAN 1 g can cause serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions and use of the medicine should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

PERFALGAN 1 g Solution for Infusion 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.

PERFALGAN 1 g should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia), (see DOSAGE AND DIRECTIONS FOR USE, Recommended dosage in patients with hepatic impairment and PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Special populations, Hepatic impairment).
- Severe renal insufficiency (creatinine clearance ≤ 30ml/min) (see DOSAGE AND DIRECTIONS FOR USE and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).
- 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, hypovolaemia.

Store in a safe place out of reach of children.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease should not use excessive quantities of PERFALGAN 1 g.

Use with caution in renal disease.

Mannitol:

PERFALGAN 1 g contains mannitol and may have a laxative effect.

INTERACTIONS:

Effect of other medicines on PERFALGAN 1 g:

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the PERFALGAN 1 g dose should be considered when administered concomitantly with probenecid.
- Salicylamide may prolong the elimination half-life of paracetamol as contained in PERFALGAN 1 g.
- Caution should be paid to the concomitant use of PERFALGAN 1 g and enzyme-inducing substances as these substances increase the risk of paracetamol induced liver injury. These substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, and ethanol (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).
- Phenytoin administered concomitantly with PERFALGAN 1 g 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.
- 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.

Effect of PERFALGAN 1 g on other medicines:

- PERFALGAN 1 g may increase the chance of unwanted effects when administered with other medicines.
- Anticoagulants: Concomitant use of PERFALGAN 1 g (4 g per day for at least 4 days) with coumarins including warfarin may lead to variations in INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after PERFALGAN 1 g treatment has been discontinued.

PREGNANCY AND LACTATION:

Pregnancy:

Clinical experience of intravenous administration of PERFALGAN 1 g 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.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any teratogenic or foetotoxic effects.

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

Lactation:

After oral administration, paracetamol is excreted into breast milk in small quantities. Rash in nursing infants has been reported. Caution should be used when administering PERFALGAN 1 g to women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

DO NOT EXCEED THE RECOMMENDED DOSE

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

Unintentional overdose can lead to serious liver damage and death (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT). 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 DIRECTIONS FOR USE, Recommended dosage in patients with hepatic impairment.)

Recommended dosage in adult patients

The recommended dose in adult patients weighing more than 50 kg is:

PERFALGAN 1 g per administration (i.e. one 100 ml vial) up to 4 times a day.

The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 4 g in 24 hours.

The recommended dose in adult patients weighing less than 50 kg and more than 33 kg (approximately 11 years old) is:
PERFALGAN 1 g: 15 mg/kg per administration (i.e. 1,5 ml solution per kg) up to 4 times per day. The minimum interval between each administration must be 4 hours. For these adult underweight patients, the maximum daily dose must not exceed 60 mg/kg and must not exceed 3 g in 24 hours.

Recommended dosage in paediatric and adolescent patients

The 100 ml vial is restricted to adults, adolescents, and children weighing more than 33 kg.

DOSING IS BASED ON PATIENT WEIGHT

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.

Recommended dosage in patients with renal impairment

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 PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Recommended dosage in patients with hepatic impairment

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

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

Method of administration

General

For all patients, PERFALGAN 1 g 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.

As PERFALGAN 1 g is presented in glass vials, close monitoring to avoid air embolism is needed, notably at the end of the infusion, regardless of the route of administration but especially if a central venous catheter is used for the infusion.

Any unused solution should be discarded.

PERFALGAN 1 g should not be mixed with other medicinal products.

SIDE EFFECTS:

Adverse reactions to PERFALGAN 1 g are rare (≥ 1/10 000 to < 1/1 000) or very rare (< 1/10 000) as described below:

Organ System	**Rare** ≥ 1/10 000 to < 1/1 000	**Very rare** < 1/10 000
General disorders and administration site condition	Malaise	Hypersensitivity

Cardiac disorders	Hypotension	
Hepatobiliary disorders	Increased levels of hepatic transaminases	Hepatitis, pancreatitis
Blood and lymphatic system disorders		Thrombocytopenia, agranulocytosis, leucopenia, pancytopenia, neutropenia, anaemia
Renal and urinary disorders		Renal colic, renal failure and sterile pyuria

Postmarketing experience:

The following adverse events have also been reported during postmarketing surveillance but the incidence rate (frequency) is not known.

Organ System	Adverse event
Blood and lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Nausea Vomiting
General disorders and administration site condition	Administration site reaction
Hepatobiliary disorders	Fulminant hepatitis Hepatic necrosis Hepatic failure Increased hepatic enzymes
Immune system disorders	Anaphylactic shock

	Anaphylaxis Hypersensitivity reaction Angio-oedema
Skin and subcutaneous tissue disorders	Erythema Flushing Pruritus Rash Urticaria Acute generalised exanthematous pustulosis Toxic epidermal necrolysis Stevens-Johnson syndrome

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS)

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 PERFALGAN 1 g 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 poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition, AIDS and with the use of drugs 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 poisoning 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 /INR. Liver damage may lead to encephalopathy, coma and death.

Overdose with a single administration of 7,5 g or more of paracetamol in adults or 140 mg/kg of body weight 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.

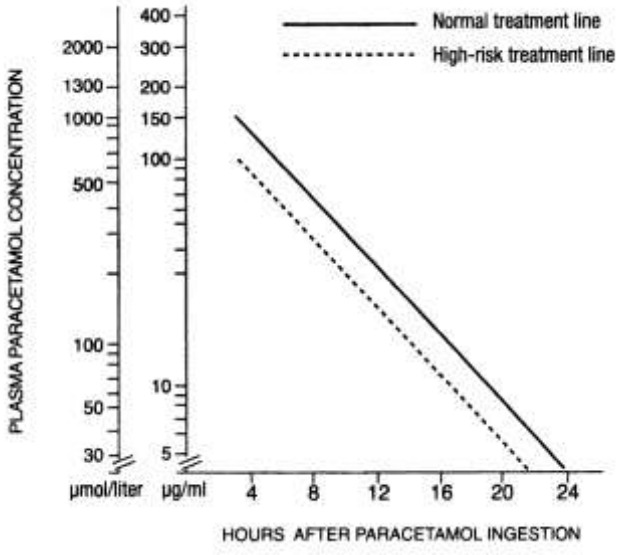
Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms

of liver damage are usually evident initially after two days and reach a maximum after 4 to 6 days.

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 of PERFALGAN 1 g overdosage:

- 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 injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. 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.



Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed.

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 ingestion for at least 96 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

IDENTIFICATION:

The solution for infusion is clear and slightly yellowish.

PRESENTATION:

PERFALGAN 1 g is available in 100 ml clear Type II glass vials in packs of 12 vials.

STORAGE INSTRUCTIONS:

Store at or below 30˚C.

Do not refrigerate or freeze. Once opened, the vial should be used immediately. Any unused portion should be discarded. Keep out of reach and sight of children.

REGISTRATION NUMBER:

PERFALGAN 1 g: A38/2.7/0561

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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