PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAMES AND DOSAGE FORM

PARACETAMOL FRESENIUS 10 mg/ml (50 ml) (solution for intravenous infusion)

PARACETAMOL FRESENIUS 10 mg/ml (100 ml) (solution for intravenous infusion)

COMPOSITION

PARACETAMOL FRESENIUS 10 mg/ml (100 ml): Each 100 ml bottle contains 1 g of paracetamol.

PARACETAMOL FRESENIUS 10 mg/ml (50 ml): Each 50 ml bottle contains 0,5 g of paracetamol.

Inactive ingredients:

Mannitol, water for injection, nitrogen

Contains 0,01 % *m/v* cysteine (as antioxidant)

Osmolality: 280 mOsm/l

PHARMACOLOGICAL CLASSIFICATION

A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

PHARMACOLOGICAL ACTION

Paracetamol has analgesic and antipyretic activities.

Pharmacodynamic properties:

Paracetamol has centrally and peripherally acting analgesic and antipyretic properties. The mechanism of action has not been established.

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 approximately 30 µg/ml.

Distribution:

The volume of paracetamol distribution is about 1 l/kg. Paracetamol does not bind extensively to plasma proteins. After the infusion of 1 g of paracetamol in adults, significant concentrations of paracetamol was observed in the cerebrospinal fluid after about 20 minutes (about 1,5 µg/ml).

Metabolism:

Paracetamol is metabolised mostly by the liver through two major pathways: glucuronic acid conjugation and sulphuric acid conjugation. The sulphuric acid conjugation pathway is highly saturable at doses that exceed the recommended therapeutic doses. A small amount (less than 4 %) is metabolised by cytochrome P450 to a reaction intermediate (N-acetyl benzoquinoneimine) which, under normal conditions of use is quickly 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 highly increased.

Elimination:

Paracetamol metabolites are mainly excreted in the urine, of which 90 % of the dose is excreted within 24 hours. Less than 5 % is excreted unchanged, the rest as glucuronide (± 70 %) and sulphate (± 25 %) conjugates.

Total body clearance of paracetamol is 18 l/hour and plasma elimination half-life is about 2,7 hours.

Special populations:

The only pharmacokinetic parameters of paracetamol different in children than in adults are the plasma half-life which is slightly shorter (± 2 hours).

The total excretion rate of paracetamol stays the same at all ages.

Patients with renal insufficiency:

The elimination half-life of paracetamol is significantly impaired (± 2 – 5,3 hours) in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min). The elimination of the conjugates, glucuronide and sulphate is up to three times slower than in normal patients.

It is therefore recommended that the dose interval between administrations be at least 6 hours in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see **Dosage and directions for use**).

Elderly patients:

No dose adjustment is required for elderly patients as the pharmacokinetics and metabolism of paracetamol do not change in these patients.

INDICATIONS

Short-term treatment of mild to moderate pain e.g. after dental procedures and minor orthopaedic surgery and the short-term treatment of fever when the oral route of administration is unsuitable.

CONTRAINDICATIONS

PARACETAMOL FRESENIUS 10 mg/ml should not be used in:

- Patients that are hypersensitive to paracetamol, pro-paracetamol hydrochloride (pro-drug of paracetamol), or any of the excipients of PARACETAMOL FRESENIUS 10 mg/ml.
- Patients with severe hepatocellular insufficiency, or active liver disease including alcoholic hepatitis.

WARNINGS AND SPECIAL PRECAUTIONS

It is highly recommended to use the oral route of administration as soon as it is available.

To avoid the chance of overdose, check that any other medicines also used do not contain paracetamol.

PARACETAMOL FRESENIUS 10 mg/ml contains paracetamol, which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the patient may be asymptomatic, the nearest doctor, hospital, or Poison Control Centre should be contacted immediately.

Higher doses than recommended can cause severe liver damage. The clinical signs of hepatic damage are usually seen first after 2 days with maximum damage seen after 4 – 6 days. Treatment with the antidote should be started as soon as possible (see **Known symptoms of overdosage and particulars of its treatment**).

PARACETAMOL FRESENIUS 10 mg/ml should be used with caution in patients with mild to moderate liver impairment and it is contraindicated where there is active disease, particularly in alcoholic hepatitis. Patients recovering from liver damage should not be given high doses of PARACETAMOL FRESENIUS 10 mg/ml.

PARACETAMOL FRESENIUS 10 mg/ml should also be used with caution in the following cases:

- Patients with renal damage or disease.
- Patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see **Dosage and directions for use** and **Pharmacokinetic properties**).
- Hepatocellular insufficiency.

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency which may lead to haemolytic anaemia.
- Chronic alcoholism, excessive alcohol intake.
- Chronic malnutrition, anorexia, bulaemia, cachexia (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia.

Effect on the ability to drive and use machines:

PARACETAMOL FRESENIUS 10 mg/ml has no influence on the ability to drive and use machines.

INTERACTIONS

- Phenytoin administered concomitantly with PARACETAMOL FRESENIUS 10 mg/ml 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 hepatotoxicity.
- Probenecid causes a significant decrease in the clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the PARACETAMOL FRESENIUS 10 mg/ml dose should be considered when administered concomitantly with probenecid.
- Salicylamide may prolong the elimination half-life of PARACETAMOL FRESENIUS 10 mg/ml.
- Concomitant intake of PARACETAMOL FRESENIUS 10 mg/ml with enzyme-inducing substances should be cautioned as these substances increase the risk of paracetamol induced liver injury. These substances include, but are not limited to barbiturates, rifampicin, isoniazid, anticoagulants, zidovudine and

chronic use of alcohol (see **Known symptoms of overdosage and particulars of its treatment**).

PREGNANCY AND LACTATION

Pregnancy:

Safety and efficacy of PARACETAMOL FRESENIUS 10 mg/ml have not been established. However, oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or the unborn child. The exposure to overdose did not increase the risk of malformation in the child.

The oral route did not show any teratogenic or foetotoxic effects.

If, after a careful risk assessment has been done, PARACETAMOL FRESENIUS 10 mg/ml is still used, the dosage and duration of treatment must be carefully monitored. In this case the dosage and duration must be observed.

Lactation:

After oral administration paracetamol is excreted into breastmilk in small quantities. No undesirable effects on breastfed infants have been reported with frequent use. However caution should be used when administering PARACETAMOL FRESENIUS 10 mg/ml to woman who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

DO NOT EXCEED THE RECOMMENDED DOSE.

For single use only.

The recommended dose in patients weighing more than 50 kg:

One 100 ml vial up to 4 times a day. The maximum dose must not exceed 4 g per day. The minimum interval time between administrations must be 4 hours.

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

15 mg/kg per administration (1,5 ml of solution per kg). The maximum dose must not exceed 60 mg/kg without exceeding a maximum daily dose of 3 g. The minimum interval time between administrations must be 4 hours.

Patients with severe renal insufficiency:

It is recommended to leave a minimum interval time of 6 hours in patients with severe renal impairment (creatinine clearance of ≤ 30 ml/min).

Patients with 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.

PARACETAMOL FRESENIUS 10 mg/ml must be administered as a 15 minute intravenous infusion.

The solution must be visibly inspected for particulate matter and discolouration. Once the vial is opened, it must be used immediately as PARACETAMOL FRESENIUS 10 mg/ml is intended for single use only. Any unused solution must be discarded.

PARACETAMOL FRESENIUS 10 mg/ml must not be mixed with any other medicinal products.

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

SIDE EFFECTS

Blood and the lymphatic system disorders

Less frequent: Thrombocytopenia, agranulocytosis, leukopenia, pancytopenia, neutropenia, anaemia.

Immune system disorders

Less frequent: Hypersensitivity, anaphylactic shock, angioedema.

Vascular disorders

Less frequent: Hypotension, flushing.

Gastrointestinal disorders

Less frequent: Nausea, vomiting, pancreatitis.

Hepato-biliary disorders

Less frequent: Increased levels of hepatic transaminases, hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis, skin rash, urticaria, erythema, pruritus.

Renal and urinary disorders

Less frequent: Renal colic, renal failure and sterile pyuria.

General disorders and administrative site conditions

Less frequent: Malaise.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **Side effects** and **Warnings and special precautions**)

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 PARACETAMOL FRESENIUS 10 mg/ml 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 medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Overdosing may be fatal in these cases.

Symptoms of overdose:

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/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 of paracetamol overdose:

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 administration may still be of benefit especially if more than 150 mg/kg of paracetamol was administered.

An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose 5 % *m/v* injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose 5 % *m/v* injection over the next four hours and then 100 mg/kg in 1 000 ml dextrose 5 % *m/v* injection over the next sixteen hours. Sodium chloride 0,9 % *m/v* may be used where dextrose 5 % *m/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.

Monitor all patients with significant overdose for 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

Clear, colourless to slightly yellowish solution free from visible particulate contamination.

PRESENTATIONS

Packed into 50 ml or 100 ml clear, colourless glass bottles with a red rubber stopper and an aluminium cap with either a tear-off tab of aluminium or a plastic lid.

10, 12 or 20 bottles of 50 ml or 100 ml each are packed with a package insert into a cardboard box.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Do not refrigerate or freeze.

Once opened, the contents should be used immediately.

Discard any unused portion.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Paracetamol Fresenius 10 mg/ml (50 ml): 45/2.7/0531

Paracetamol Fresenius 10 mg/ml (100 ml): 45/2.7/1188

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park,

2 Tonetti Street, Halfway House,

Midrand

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of last approval: 5 December 2013

Date of notification of Regulation 9 compliance: 27 May 2016