PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PARACETAMOL FRESENIUS 10 mg/ml (50 ml)

PARACETAMOL FRESENIUS 10 mg/ml (100 ml)

Strength

PARACETAMOL FRESENIUS 10 mg/ml (50 ml)

PARACETAMOL FRESENIUS 10 mg/ml (100 ml)

Pharmaceutical form

Solution for intravenous infusion

2 QUALITATIVE AND QUANTITATIVE 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.

Paracetamol Fresenius 10 mg/ml contains mannitol

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children (1 year and body mass 10 kg)

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. See section 4.2

4.2 Posology and method of administration

DO NOT EXCEED THE RECOMMENDED DOSE

The prescribed dose must be based on the patient's weight. For single use only.

Unintentional overdose can lead to serious liver damage and death (See section 4.9) 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 section 4.8)

For Paediatric use:

Restricted to children weighing more than 10 kg (approximately 1 year of age) but less than 33 kg (approximately 11 years old).

Recommended dosage in adult patients:

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

PARACETAMOL FRESENIUS 10 mg/ml 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:

PARACETAMOL FRESENIUS 10 mg/ml: 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.

ADULT PATIENTS: 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 paediatric and adolescent patients

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

PAEDIATRIC AND ADOLESCENT PATIENTS: 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**
> 10 kg and ≤ 33 kg	15 mg/kg (ie. 1,5 ml solution per kg) up to 4 times a day	4 hours	≤ 60 mg/kg Must not exceed 2 g in 24 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 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, **PARACETAMOL FRESENIUS 10 mg/ml** 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 **PARACETAMOL FRESENIUS 10 mg/m**l 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.

PARACETAMOL FRESENIUS 10 mg/ml should not be mixed with other medicines.

PARACETAMOL FRESENIUS 10 mg/ml may be diluted up to one-tenth (one volume **PARACETAMOL FRESENIUS 10 mg/ml** into nine volumes diluent) in 0,9 % sodium chloride solution or a 5 % glucose solution. The volume of the diluted solutions should take into account the total volume of fluid to be administered to the patient as well as the medical condition of the patient.

When **PARACETAMOL FRESENIUS 10 mg/ml** (50 ml vial) is diluted as recommended, the total volume of diluted solution to be administered must be infused within one hour of its preparation (infusion time included)

4.3 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.

4.4 Special warnings and precautions for use

Warnings

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. 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 section 4.9

PARACETAMOL FRESENIUS 10 mg/ml can cause serious skin reactions such as acute generalized 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.

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.

Patients recovering from liver damage should not be given high doses of **PARACETAMOL FRESENIUS 10 mg/ml**.

PARACETAMOL FRESENIUS 10 mg/ml should be used with caution in patients with renal damage of disease.

Special precautions:

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.

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 section 4.9 and
- Hepatocellular insufficiency, including Gilert's syndrome (familial hyperbilirubinaemia)

See sections 4.2 and section 5

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency which may lead to haemolytic anaemia.
- Chronic alcoholism, 3 or more alcoholic drinks every day.
- Chronic malnutrition, anorexia, bulaemia, cachexia (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia.
- "**PARACETAMOL FRESENIUS 10 mg/ml** contains mannitol and may have a laxative effect."

4.5 Interaction with other medicines and other forms of interaction

- 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 section 4.9
- 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 PARACETAMOL FRESENIUS 10 mg/ml on other medicines:

- **PARACETAMOL FRESENIUS 10 mg/ml** may increase the chance of unwanted effects when administered with other medicines.
- Anticoagulants: Concomitant use of **PARACETAMOL FRESENIUS 10 mg/ml** (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 **PARACETAMOL FRESENIUS 10 mg/ml** treatment has been discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Clinical experience of intravenous administration of **PARACETAMOLFRESENIUS 10 mg/ml** 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, **PARACETAMOL FRESENIUS 10 mg/ml 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 breastmilk in small quantities. Rash in nursing infants has been reported. 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Blood and the lymphatic system disorders

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

Immune system disorders

Less frequent: Hypersensitivity, anaphylactic shock, angioedema.

Cardiac disorders

Frequency unknown: Tachycardia, Hypotension

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.

Frequency unknown: Fulminant hepatitis, pancreatitis

Skin and subcutaneous tissue disorders

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

Acute generalised exanthematous pustulosis, Toxic epidermal necrolysis Stevens-Johnson syndrome

Frequency unknown: Flushing

Renal and urinary disorders

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

General disorders and administrative site conditions

Less frequent: Malaise, administration site reactions, hypersensitivity.

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. Health care 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

4.9 Overdose

See sections 4.4 and 4.8

Overdosage with paracetamol (including **PARACETAMOL FRESENIUS 10 mg/ m**l) can result in severe liver damage and sometimes acute renal tubular necrosis. 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. 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.

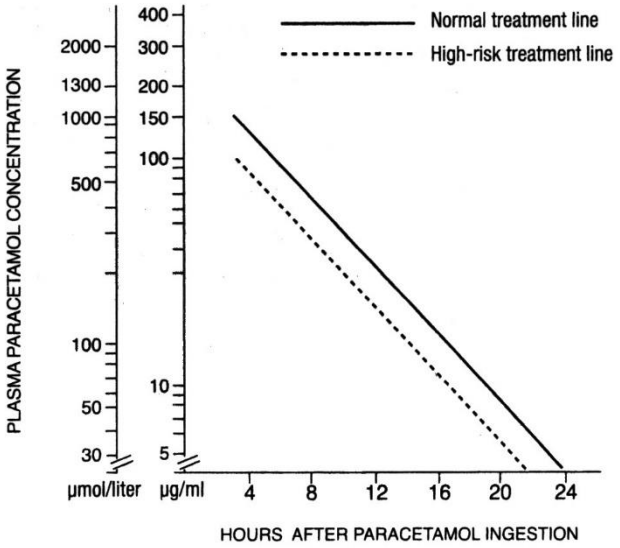
Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days and reach 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 PARACETAMOL FRESENIUS 10 mg/ml 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.



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 the paracetamol nomogram above)*. Prothrombin index correlates best with survival.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

Paracetamol has analgesic and antipyretic activities.

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

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 (Cmax) 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 were 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.

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:

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 section 4.2

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 section 4.3

Elderly patients:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injection, nitrogen

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

Osmolality: 280 mOsm/l

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Not Applicable

6.4 Special precautions for storage

Store at or below 30 °C.

Do not refrigerate or freeze.

Once opened, the contents should be used immediately.

Discard any unused portion.

After dilution in 0,9 % sodium chloride: do not store for more than 1 hour (infusion time included).

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

No special precaution required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park,

2 Tonetti Street, Halfway House,

Midrand

8 REGISTRATION NUMBERS

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

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

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 December 2013

10 DATE OF REVISION OF THE TEXT

26 November 2021