Approved professional information for MANNITOL 20 % FRESENIUS

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MANNITOL 20 % FRESENIUS

Solution for infusion (parenteral).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500 ml solution contains 100 g of mannitol.

Contains sugar (mannitol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (parenteral).

A clear colourless or almost colourless solution. Crystals might be present which will dissolve on warming to 37 °C.

Osmolarity: 1 098 mOsm/l

pH (approx.) 6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapeutic use.

MANNITOL 20 % FRESENIUS is indicated for:

- The promotion of diuresis, in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established.
- The reduction of intracranial pressure and treatment of cerebral oedema by reducing brain mass.
- The reduction of elevated intraocular pressure and volume of cerebrospinal fluids when the pressure cannot be lowered by other means.
- Promoting the urinary excretion of toxic substances.
- If given in sufficiently large amounts, MANNITOL 20 % FRESENIUS increases extracellular osmolarity, which in turn may decrease cellular swelling and improve renal blood flow.
- For the evaluation of acute oliguria.

4.2 Posology and method of administration

For intravenous use only.

Warm before use to dissolve crystals. Do not use unless solution is clear. Use filter type administration set.

The adult dose for promotion of diuresis ranges from 50 to 200 g over a 24 hour period of infusion; the rate is generally adjusted to maintain a urinary output of at least 30 to 50 ml per hour. It should be preceded by a test dose in patients with marked oliguria or questionable adequacy of renal function. The recommended test dose is 200 mg/kg (approximately 75 ml MANNITOL 20 % FRESENIUS OR 60 ml MANNITOL 25 % FRESENIUS for an adult patient), infused over 3 to 5 minutes. If the first or a second test dose fails to promote a urinary flow

greater than 30 ml per hour for 2 to 3 hours, the patient's status should be re-evaluated prior to continuation of therapy. When used for the prevention of acute renal failure during various types of surgery or for the treatment of oliguria, the total dose is 50 to 100 g of mannitol for an adult patient. The dose for the reduction of intracranial pressure and brain mass prior to neurosurgery, or for the reduction of intraocular tension during an acute attack of congestive glaucoma or for ophthalmic surgery, is 1,5 to 2 g/kg given as a 20 % solution over a period of 30 to 60 minutes.

4.3 Contraindications

- Hypersensitivity to mannitol or to any of the excipients listed in section 6.1.
- Renal disease of sufficient severity to produce anuria and marked pulmonary congestion.
- MANNITOL 20 % FRESENIUS is contraindicated in patients with pulmonary congestion or oedema, intracranial bleeding (except during craniotomy), metabolic oedema with abnormal capillary fragility, severely dehydrated patients, or patients with renal failure unless a test dose has produced a diuretic response.
- MANNITOL 20 % FRESENIUS is also contraindicated in patients with congestive heart failure because in patients with diminished cardiac reserve, expansion of the extracellular fluid may lead to fulminating heart failure.
- MANNITOL 20 % FRESENIUS should not be administered with whole blood.
- Progressive renal damage or dysfunction after the institution of mannitol therapy, including oliguria and azotaemia.
- Pre-existing plasma hyperosmolarity.
- Disturbance of the blood-brain barrier.

4.4 Special warnings and precautions for use

MANNITOL 20 % FRESENIUS is a hyperosmolar solution. This solution may not be mixed with other products.

Hyperosmotic solutions of MANNITOL 20 % FRESENIUS should be administered slowly by intravenous injection and should not be mixed with blood in the transfusion apparatus.
MANNITOL 20 % FRESENIUS contains mannitol and may have a laxative effect.

Hypersensitivity

Anaphylactic/anaphylactoid reactions, including anaphylaxis, as well as other hypersensitivity/infusion reactions have been reported with MANNITOL 20 % FRESENIUS. Fatal outcome has been reported (see section 4.8).
The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develops.
Appropriate therapeutic countermeasures must be instituted as clinically indicated.
Mannitol occurs in nature (e.g. in some fruits and vegetables) and is widely used as an excipient in medicines and cosmetics. Therefore, patients may be sensitised without having received intravenous treatment with MANNITOL 20 % FRESENIUS.

CNS toxicity

CNS toxicity manifested by confusion, lethargy and/or coma has been reported in patients treated with MANNITOL 20 % FRESENIUS, in particular in the presence of impaired renal function. Fatal outcomes have been reported.

CNS toxicity may result from:

- high serum mannitol concentrations
- serum hyperosmolarity resulting in intracellular dehydration within the CNS
- hyponatraemia or other disturbances of electrolyte and acid/base balance secondary to mannitol administration.

At high concentrations, mannitol may cross the blood-brain barrier and interfere with the ability of the brain to maintain the pH of the cerebrospinal fluid especially in the presence of acidosis.

In patients with pre-existing compromised blood-brain barrier, the risk of increasing cerebral oedema (general or focal) associated with repeated or continued use of mannitol must be individually weighed against the expected benefits.

A rebound increase of intracranial pressure may occur several hours after the use of mannitol. Patients with compromised blood-brain barrier are at increased risk.

Risk of renal complications

Reversible, acute oligoanuric renal failure has occurred in patients with normal pre-treatment renal function who received large intravenous doses of MANNITOL 20 % FRESENIUS.

Although the osmotic nephrosis associated with MANNITOL 20 % FRESENIUS administration is in principle reversible, osmotic nephrosis in general is known to potentially proceed to chronic or even end-stage renal failure.

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic medicinal products, are at increased risk of renal failure following administration of MANNITOL 20 % FRESENIUS. Serum osmolar gap and renal function should be closely monitored and appropriate action initiated, should signs of worsening renal function or haematuria appear.

MANNITOL 20 % FRESENIUS should be administered with caution to patients with severely impaired renal function. A test dose should be employed and therapy with mannitol continued only if an adequate urine flow is achieved (see section 4.2).

If the urine output declines or haematuria is observed during MANNITOL 20 % FRESENIUS infusion, the patient's clinical status should be closely reviewed for developing renal impairment, and the mannitol infusion suspended, if necessary.

Risk of hypervolaemia

The cardiovascular status of the patient should be carefully evaluated before rapidly administering MANNITOL 20 % FRESENIUS.

High doses and/or high rates of infusion, as well as accumulation of mannitol (due to insufficient renal excretion of mannitol), may result in hypervolaemia, overexpansion of the extracellular fluid, which may lead to or exacerbate existing congestive heart failure.

Accumulation of mannitol may result if urine output continues to decline during administration and this may worsen existing or latent congestive heart failure.

The infusion of MANNITOL 20 % FRESENIUS should be terminated if the patient develops signs of progressive renal dysfunction, heart failure or pulmonary congestion. The expansion of extracellular volume can precipitate pulmonary oedema and patients with diminished cardiac reserve are at special risk.

Risk of water and electrolyte imbalances and hyperosmolarity

Mannitol-induced osmotic diuresis may cause or worsen dehydration/hypovolaemia and haemoconcentration.

Acute water toxicity and hyperosmolarity may follow the intravenous administration of MANNITOL 20 % FRESENIUS if renal flow is inadequate. Patients should be closely observed for signs of electrolyte and fluid imbalance and renal function should be monitored.

Should patient serum osmolarity increase during treatment, the effects of mannitol on diuresis and reduction of intracranial and intraocular pressure may be impaired.

In addition, depending on dosage and duration of administration, electrolyte and acid/base imbalances may result from transcellular shifts of water and electrolytes, osmotic diuresis and/or other mechanisms. Such imbalances may be severe and potentially fatal.

Imbalances that may result from MANNITOL 20 % FRESENIUS treatment include:

- hypernatraemia, dehydration and haemoconcentration (resulting from excessive water loss).

Hyponatraemia

A shift of sodium-free intracellular fluid into the extracellular compartment following MANNITOL 20 % FRESENIUS infusion may lower serum sodium concentration and aggravate pre-existing hyponatraemia. Loss of sodium and potassium in the urine increases.

Hyponatraemia can lead to headache, nausea, seizures, lethargy, coma, cerebral oedema, and death. Acute symptomatic hyponatraemic encephalopathy is considered a medical emergency.

The risk for developing hyponatraemia is increased:

- in children
- in elderly patients
- in women
- post-operatively
- in persons with psychogenic polydipsia.

The risk for developing encephalopathy as a complication of hyponatraemia is increased:

- in paediatric patients (≤ 16 years of age)
- in women (in particular, premenopausal women)
- in patients with hypoxaemia
- in patients with underlying central nervous system disease.

Other electrolyte imbalances

- hypokalaemia
- hyperkalaemia
- metabolic acidosis
- metabolic alkalosis.

By sustaining diuresis, MANNITOL 20 % FRESENIUS administration may obscure and intensify inadequate hydration or hypovolaemia.

Infusion reactions

Infusion site reactions have occurred with the use of MANNITOL 20 % FRESENIUS. They include signs and symptoms of infusion site irritation and inflammation, as well as severe reactions (compartment syndrome) when associated with extravasation. See section 4.8.

Adding other medications or using an incorrect administration technique may cause febrile reactions due to possible introduction of pyrogens. In case of an adverse reaction, infusion must be stopped immediately. For information on incompatibilities and preparation of the product and additives, please see sections 6.2 and 6.6.

Volume and electrolyte replacement before use

In patients with shock and renal dysfunction, MANNITOL 20 % FRESENIUS should not be administered until volume (fluid and/or blood) and electrolytes have been replaced.

Monitoring

The acid base balance, renal function and serum osmolarity must be monitored carefully when MANNITOL 20 % FRESENIUS is used.

Patients receiving MANNITOL 20 % FRESENIUS should be monitored for any deterioration in renal, cardiac or pulmonary function and treatment discontinued in the case of adverse events.

Urinary output, fluid balance, central venous pressure and electrolyte balance (in particular serum sodium and potassium levels) should be carefully monitored.

Incompatibility with blood

MANNITOL 20 % FRESENIUS should not be given concomitantly with blood because it may cause agglutination and crenation of blood cells.

Crystallisation

When exposed to low temperatures, MANNITOL 20 % FRESENIUS may crystallise. Inspect for crystals prior to administration. If crystals are visible, re-dissolve by warming the solution up to 37 °C, followed by gentle agitation. See section 4.2.

Laboratory test interferences

MANNITOL 20 % FRESENIUS can cause false low results in some test systems for inorganic phosphorus blood concentrations.

MANNITOL 20 % FRESENIUS produces false positive results in tests for blood ethylene glycol concentrations in which mannitol is initially oxidised to an aldehyde.

Paediatric use

Safety and effectiveness in the paediatric population have not been established in clinical studies.

Geriatric use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or medicine therapy.

Risk of air embolism

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

Pressurising intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

4.5 Interaction with other medicines and other forms of interaction

MANNITOL 20 % FRESENIUS infusion should not be administered with, before or after administration of blood through the same infusion equipment.

Effect potentialisation

Concurrent use of other diuretics may potentiate the effects of MANNITOL 20 % FRESENIUS and dose adjustments may be required.

Effect inhibition

MANNITOL 20 % FRESENIUS promotes urine flow, which will mainly affect medicines that are renally reabsorbed to a large extent, thereby increasing their clearance and reducing their exposure.

MANNITOL 20 % FRESENIUS increases urinary excretion of lithium and therefore concomitant use may impair the response to lithium.

Nephrotoxicity of medicines due to fluid imbalance related to MANNITOL 20 % FRESENIUS

Although an interaction in humans is unlikely, patients receiving concomitant ciclosporin and aminoglycoside should be closely monitored for signs of nephrotoxicity.

Neurotoxic medicines

Concomitant use of neurotoxic medicines (e.g. aminoglycoside) and MANNITOL 20 % FRESENIUS may potentiate the toxicity of neurotoxic medicines. (See also section 4.4.)

Medicines affected by electrolyte imbalances

The development of electrolyte imbalances (e.g. hyperkalaemia, hypokalaemia) associated with MANNITOL 20 % FRESENIUS administration may alter the effects of medicines that are sensitive to such imbalances (e.g. digoxin, agents that may cause QT prolongation, neuromuscular blocking medicines).

Other potential interactions are with tubocurarine and depolarising neuromuscular blocking medicines (enhancement of their effects by MANNITOL 20 % FRESENIUS), oral anticoagulants (MANNITOL 20 % FRESENIUS may reduce their effects by increasing the concentration of clotting factors secondary to dehydration) and digoxin (if hypokalaemia follows mannitol treatment there is a risk of digoxin toxicity).

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

4.7 Effects on ability to drive and use machines

There is no information of the effects of MANNITOL 20 % FRESENIUS on the ability to operate a vehicle or other heavy machinery.

4.8 Undesirable effects

Immune system disorders

Frequency unknown:

Allergic reaction, anaphylactic reaction including anaphylactic shock.

Metabolism and nutrition disorders

Frequency unknown:

Fluid and electrolyte imbalance, dehydration, oedema, circulatory overload, metabolic acidosis and electrolyte loss.

Nervous system disorders

Frequency unknown:

Headache, dizziness and rebound intracranial pressure increase.

Central nervous system symptoms including convulsions, coma, confusion and lethargy.

Eye disorders

Frequency unknown:

Blurred vision.

Cardiac disorders

Frequency unknown:

Cardiac dysrhythmia, congestive heart failure, palpitations, tachycardia and angina-like chest pains.

Vascular disorders

Frequency unknown:

Hypotension and hypertension.

Respiratory, thoracic and mediastinal disorders

Frequency unknown:

Pulmonary oedema and rhinitis.

Gastrointestinal disorders

Frequency unknown:

Dryness of mouth, thirst, nausea and vomiting.

Skin and subcutaneous tissue disorders

Frequency unknown:

Urticaria and skin necrosis.

Musculoskeletal and connective tissue disorders

Frequency unknown:

Arm pain and cramps.

Renal and urinary disorders

Frequency unknown:

Excessive diuresis, osmotic nephrosis, urinary retention, acute renal failure, azotaemia, anuria, haematuria, oliguria and polyuria.

General disorders and administration site conditions

Frequency unknown:

Chills, fever, asthenia, malaise, tissue dehydration, infusion site reactions including infusion thrombophlebitis, infusion site inflammation, infusion site pain, infusion site rash, infusion site erythema, infusion site pruritis and compartment syndrome (associated with extravasation and swelling at the injection site).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of MANNITOL 20 % FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of MANNITOL 20 % FRESENIUS. 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.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Symptoms: Hypotension, polyuria that rapidly converts to oliguria, stupor, convulsions, pulmonary oedema, hyperosmolarity and hyponatraemia.

Treatment: Discontinue infusion immediately. Institute supportive measures to correct fluid and electrolyte imbalances. Haemodialysis is beneficial to clear mannitol and reduce serum osmolarity.

See sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.1 Diuretics.

Pharmacotherapeutic group: Solutions producing osmotic diuresis.

ATC code: B05BC01.

Mannitol is an osmotic diuretic. It is freely filterable at the glomerulus, undergoes limited reabsorption by the renal tubule and is pharmacologically inert by conventional criteria. These three characteristics permit the administration of this agent in sufficiently large quantities to contribute significantly to the osmolality of the plasma, the glomerular filtrate and the tubular fluid.

The action within the kidney depends primarily upon the concentration of osmotically active particles in solution.

An additional action of the osmotic diuretics is to increase the rate of electrolyte excretion, particularly sodium, chloride and potassium. However, this occurs only with large doses.

5.2 Pharmacokinetic properties

When administered intravenously, mannitol is eliminated largely unmetabolised through the glomeruli. Only 10 % is reabsorbed back from the kidney tubule. The elimination half-life in adults is approximately 2 hours, longer where renal failure is present. 80 % of an intravenous dose is excreted unchanged within 3 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injection.

6.2 Incompatibilities

MANNITOL 20 % FRESENIUS should not be administered with whole blood.

MANNITOL 20 % FRESENIUS is a hyperosmolar solution. This solution may not be mixed with other products.

6.3 Shelf life

PVC bags: 24 months at or below 25 °C.

free*flex*® bags: 24 months at or below 30 °C.

Kabipac bottles: 36 months at 25 °C.

6.4 Special precautions for storage

PVC bags and Kabipac bottles: store at or below 25 °C.

free*flex*® bags: store at or below 30 °C.

6.5 Nature and contents of container

500 ml flexible PVC/**free***flex*® bags or 500 ml or 1 000 ml polyethylene bottles (Kabipac).

Pack sizes:

1, 18 or 20 PVC/**free***flex*® bags or Kabipac bottles are packed in a corrugated cardboard shipper box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use filter type administration set.

Warm before use to dissolve crystals.

Do not use if solution is cloudy or if there is a deposit.

Check for minute leaks by squeezing bag.

Destroy any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten 6020

Gqeberha

South Africa

8. REGISTRATION NUMBER

L/18.1/228

9. DATE OF FIRST AUTHORISATION

30 January 1979

10. DATE OF REVISION OF THE TEXT

26 May 2022