



SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE MEDICINAL PRODUCT

DELEFLUIDS MANNITOL 10% w/v INTRAVENOUS INJECTION BP 500ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ingredients	Quantity/Tablet (g)	Quantity/Batch (Kg)	Specification	%
Mannitol 10%	10	210	BP.	100
Purified Water	q.s	2100ltrs	BP.	100

BP: British Pharmacopoeia (current edition)

3. PHARMACEUTICAL FORM

Injectable

Description:

Clear, Colourless transparent liquid contains in 500ml PVC Pouch

Osmolarity : 549 mOsm/l (approx)

pH : 4.5 – 7.0

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Delefluids Mannitol 10% Solution for infusion is indicated for use as an osmotic diuretic in the following situations:

- Promotion of diuresis in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established.
- Reduction of intracranial pressure and cerebral oedema, when blood-barrier is intact.
- Reduction of elevated intraocular pressure when it cannot be lowered by other means.
- Promotion of elimination of renally excreted toxic substances in poisoning.

4.2 Posology and method of administration

Posology:

The choice of the specific mannitol concentration, dosage and rate of administration depends on the age, weight, clinical and biological condition of the patient and concomitant therapy.

Adults and adolescents:

Acute renal failure

The general dose range is 50 to 200 g mannitol (500 ml to 2000 ml/day) in a 24 hour period, with a dosage limit of 50 g (500ml mannitol) on any one occasion. In most instances, adequate response will be achieved at a dosage of 50 to 100 g mannitol/day (500 ml to 1000 ml /day).

The rate of administration is usually adjusted to maintain a urine flow of at least 30-50 ml/hour.

Only in emergency situations, the maximum infusion rate can be as high as 200 mg/kg infused over 5 minutes (see also test dose). After 5 minutes, the infusion rate should be readjusted to maintain a urine flow of at least 30-50 ml/hour, with a maximal dose of 200 g/24h.

Use in patients with oliguria or renal impairment

Patients with marked oliguria or suspected inadequate renal function should first receive a test dose of approximately 200 mg mannitol/kg bw (body weight) (2ml/kg bw) over a period of 3 to 5 minutes. For example: in an adult patient with a body weight of 70 kg: approximately 75 ml of a 20% solution or 100 ml of a 15% solution. The response to the test dose is considered adequate if at least 30-50 ml/hour of urine is excreted for 2-3 hours. If an adequate response is not attained, a further test dose may be given. If an adequate response to the second test dose is not attained, treatment with mannitol should be discontinued and the patient reassessed as established renal failure may be present.

Reduction of intracranial pressure, cerebral volume and intraocular pressure

The usual dose is 1.5 to 2g/kg bw (15 to 20 ml/kg bw), infused over 30 to 60 minutes. When used preoperatively, the dose should be administered 1 to 1.5 hours before surgery to obtain the maximum effect.

Promotion of elimination of renally excreted toxic substances in poisoning

In forced diuresis, the dose of mannitol should be adjusted to maintain urinary output of at least 100ml/hour and positive fluid balance of 1-2 litres. An initial loading dose of approximately 25 g (250 ml) may be given.

Paediatric population:

In renal insufficiency, the test dose should be 200 mg mannitol/kg bw (2 ml/kg bw) over 3-5 minutes. The treatment dose ranges from 0.5 to 1.5 g/kg bw (5 ml/kg bw to 15 ml/kg bw). This dose may be repeated once or twice, after an interval of 4 to 8 hours, if necessary.

For cerebral and ocular oedema, this dose may be given over 30 to 60 minutes as for adults.

Elderly population:

As for adults, the dosage depends on the weight, clinical and biological condition of the patient and concomitant therapy. The general dose range is the same as for adults, 50 to 200 g in a 24 hour period (500 ml to 2000ml/day), with a dosage limit of 50 g mannitol (500 ml) on any one occasion. Since incipient renal insufficiency may be present, caution should be used when reviewing patient's status prior to dose selection.

Method of administration:

The solution is for intravenous administration through sterile and non-pyrogenic equipment.

Hyperosmolar mannitol solutions may cause vein damage. Check product's osmolality before administration.

Use administration set which includes a final in-line filter because of the potential for mannitol crystals to form and using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

Use only if the solution is clear, without visible particles or discoloration and the seal is intact. Confirm the integrity of the bag. Use only if the container is undamaged. Administer immediately following insertion of the infusion set.

This hypertonic solution should be administered via a large peripheral or preferably a central vein. Rapid infusion in peripheral veins may be harmful.

Mannitol solutions may crystallize when exposed to low temperature. At higher concentrations, the solutions have a greater tendency to crystallize. Inspect for crystals prior to administration. If crystals are visible, re-dissolve by warming the solution up to 37°C followed by gentle agitation. Solutions should not be heated in water or in a microwave oven due to the potential for product contamination or damage. Only dry heat (for example: a warming cabinet) should be used. Allow the solution to cool to room or body temperature before re-inspection for crystals and use. Please see also sections 4.4 and 6.6.

For information on incompatibilities and preparation of the product and additives, please see sections 6.2 and 6.6.

4.3 Contraindications

Mannitol 10% Solution for Infusion is contra-indicated in patients presenting with:

- Pre-existing plasma hyperosmolality.
- Severe dehydration.
- Well established anuria.
- Severe heart failure.
- Severe pulmonary congestion or pulmonary oedema.
- Active intracranial bleeding, except during craniotomy.
- Disturbance of the blood-brain barrier.
- Hypersensitivity to mannitol.

4.4 Special warnings and precautions for use

Hypersensitivity

Anaphylactic/anaphylactoid reactions, including anaphylaxis, as well as other hypersensitivity/infusion reactions have been reported with mannitol. 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 develop. 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 excipient in drugs and cosmetics. Therefore, patients may be sensitized without having received intravenous treatment with mannitol.

CNS toxicity

CNS toxicity manifested by, e.g. confusion, lethargy, and coma has been reported in patients treated with mannitol, 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.

Progressive renal damage or dysfunction, after institution of mannitol therapy, including increasing oliguria and azotemia, has also been described.

Although the osmotic nephrosis associated with mannitol 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 drugs, are at increased risk of renal failure following administration of mannitol. Serum osmolar gap and renal function should be closely monitored and appropriate action initiated, should signs of worsening renal function appear.

Mannitol 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 during mannitol 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 10% Solution for Infusion.

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 intensify existing or latent congestive heart failure.

If the patient's cardiac or pulmonary function deteriorates, treatment should be discontinued.

Risk of water and electrolyte imbalances, hyperosmolarity

Mannitol-induced osmotic diuresis may cause or worsen dehydration/hypovolaemia and hemoconcentration. Administration of mannitol may also cause hyperosmolarity.

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 treatment include:

- Hypernatraemia, dehydration and hemoconcentration (resulting from excessive water loss).
- Hyponatraemia (Shift of sodium-free intracellular fluid into the extra cellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatraemia. Sodium may be lost in the urine).

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, for example:

- In children.
- In elderly patients.
- In women.
- Postoperatively.
- In persons with psychogenic polydipsia.

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

- 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.

Hypokalaemia, hyperkalaemia, other electrolytes imbalances, metabolic acidosis and metabolic alkalosis.

Mannitol may obscure and intensify inadequate hydration and hypovolaemia.

Infusion reactions

Infusion site reactions have occurred with the use of mannitol. 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 the 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 should not be administered until volume (fluid, blood) and electrolytes have been replaced.

Monitoring

The acid base balance, renal function and serum osmolarity must be monitored carefully when mannitol is used.

Patients receiving mannitol 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 should not be given concomitantly with blood because it may cause agglutination and crenation of blood cells.

Crystallization

When exposed to low temperatures, solutions of mannitol may crystallize. Inspect for crystals prior to administration. If crystals are visible, redissolve by warming the solution up to 37°C followed by gentle agitation. See section 4.2.

Laboratory test interferences

Mannitol can cause false low results in some tests systems for inorganic phosphorus blood concentrations.

Mannitol produces false positive results in tests for blood ethylene glycol concentrations in which mannitol is initially oxidized 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 drug 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.

Pressurizing intravenous solutions, contained in flexible plastic containers, in order 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 medicinal products and other forms of interaction

Effect Potentialisation

Concurrent use of other diuretics may potentiate the effects of mannitol and dose adjustments may be required.

Effect Inhibition

Mannitol promotes urine flow, which will mainly affect drugs that are renally reabsorbed to a large extent - thereby increasing their clearance and reducing their exposure.

Mannitol increases urinary excretion of lithium and therefore concomitant use of mannitol may impair the response to lithium.

Nephrotoxicity of drugs due to fluid imbalance related to mannitol

Patients receiving concomitant ciclosporin and aminoglycoside should be closely monitored for signs of nephrotoxicity.

Neurotoxic agents

Concomitant use of neurotoxic agents (e.g. aminoglycoside) and mannitol may potentiate the toxicity of neurotoxic agents. (See also section 4.4).

Agents affected by electrolyte imbalances

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

Other potential interactions are with tubocurarine and depolarising neuromuscular blocking drugs (enhancement of their effects by mannitol), oral anticoagulants (mannitol 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), although there is limited evidence of such interactions occurring in humans.

4.6 Fertility, pregnancy and lactation

There are no adequate published data from the use of mannitol in pregnant women.

There are no adequate published data, from animal studies, with respect to mannitol's effect on pregnancy and/or embryo/foetal development and/or parturition and/or postnatal development.

Mannitol should not be used during pregnancy unless clearly needed.

There is no information on excretion of mannitol in breast milk.

Mannitol should not be used during lactation unless clearly necessary.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following adverse reactions have been reported in post-marketing experience. The frequency of the adverse drug reactions listed in this section cannot be estimated from the available data.

MedDRA System Organ Class	Adverse reaction (MedDRA Preferred Term)	Frequency
Immune system disorders	Allergic reaction Anaphylactic reaction including anaphylactic shock that can be manifested with skin, gastrointestinal, and severe circulatory (hypotension) and respiratory manifestations (e.g. dyspnea). Other hypersensitivity/infusion reactions, include <ul style="list-style-type: none">• hypertension• pyrexia• chills• sweating• cough• musculoskeletal stiffness and myalgia• urticaria/rash• pruritus• generalized pain• discomfort• nausea• vomiting• headache	Not known
Metabolism and nutrition disorders	Fluid and electrolytes imbalance including <ul style="list-style-type: none">• hypervolaemia• peripheral oedema	Not known

	<ul style="list-style-type: none"> • dehydration • hyponatraemia • hypernatraemia • hyperkalaemia • hypokalaemia Metabolic acidosis	
Nervous system disorders	Headache Dizziness Rebound intracranial pressure increase CNS toxicity manifested by <ul style="list-style-type: none"> • Convulsions • Coma • Confusion • Lethargy 	Not known
Eye disorders	Blurred vision	Not known
Cardiac disorders	Cardiac arrhythmia Congestive heart failure	Not known
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema Rhinitis	Not known
Gastrointestinal disorders	Mouth dry Thirst Nausea Vomiting	Not known
Skin and subcutaneous tissue disorders	Skin necrosis Urticaria	Not known
Musculoskeletal and connective tissue disorders	Cramps	Not known
Renal and urinary disorders	Excessive diuresis Nephrosis osmotic Urinary retention Acute renal failure Azotemia Anuria Oliguria Polyuria	Not known
General disorders and administration site conditions	Chills Chest pain (angina-like chest pain) Fever Asthenia Malaise Infusion site reactions including <ul style="list-style-type: none"> • infusion thrombophlebitis 	Not known
		Not known

	<ul style="list-style-type: none"> • infusion site inflammation • infusion site pain • infusion site rash • infusion site erythema, infusion site pruritus • infusion site pruritus Compartment syndrome (associated with extravasation and swelling at the injection site)	
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Other adverse reactions

Severe anaphylaxis with cardiac arrest, and fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Signs and symptoms of overdose with mannitol may include acute renal failure, electrolytes imbalance, hypervolaemia, CNS toxicity.

Prolonged administration or rapid infusion of large volumes of hyperosmotic solutions may results in circulatory overload and acidosis. Headache, nausea and shivering without temperature change may represent initial signs/symptoms. Confusion, lethargy, convulsions, stupor and coma may follow.

In case of suspected overdose, treatment with mannitol should be stopped immediately.

Management is symptomatic and supportive, with monitoring of fluid and electrolyte balance. Mannitol is dialyzable. Haemodialysis may be helpful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: “Solutions producing osmotic diuresis”, ATC code: “B05BC01”

Mannitol, a carbohydrate, is confined to the extracellular compartment. It has an osmotic effect which causes fluid to pass from the intracellular to the extracellular compartment.

Mannitol is freely filterable at the kidney glomerulus and less than 10% is reabsorbed back from the kidney tubule. Confined to the kidney tubules, mannitol exerts an osmotic effect which prevents fluid reabsorption from the glomerular filtrate and produces diuresis. It thereby promotes urine flow in oliguria/anuria or in situations where the patient is at risk of onset of acute renal failure. Mannitol also increases electrolyte excretion, especially sodium, potassium and chloride. Excretion of renally excreted toxic substances such as aspirin and barbiturates is also increased.

Mannitol does not penetrate the blood-brain barrier under usual circumstances. Confined to the plasma, mannitol exerts an osmotic pressure, causing fluid to leave the brain tissue, and brain volume and intracranial pressure to be reduced.

Mannitol does not penetrate the eye. Mannitol promotes excretion of aqueous humour and thereby reduces intraocular pressure.

5.2 Pharmacokinetic properties

When administered intravenously, mannitol is eliminated largely unmetabolised through the glomeruli. It is freely filtered by the glomeruli, with less than 10% tubular reabsorption and is not secreted by tubular cells. 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.

5.3 Preclinical safety data

The preclinical safety assessment of mannitol 10% in animals is not relevant as mannitol is a substance with well-established use in patients and is covered by appropriate pharmacopoeial references.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

Additives may be incompatible with Mannitol 10% Solution for infusion.

Incompatibility of the medicinal product to be added with the solution in the container must be assessed before addition.

Before adding a medicinal product, verify it is soluble and stable in water at the pH of the mannitol solution (4.5 to 7.0)

Mannitol 10% Solution for Infusion should not be administered simultaneously with, before, or after administration of blood through the same infusion equipment, due to risk of pseudoagglutination

The Instructions for Use of the medicinal product to be added must be consulted.

As an example cefepime, imipenem, cilastin and filgrastim are incompatible with mannitol solutions, but this list is not exhaustive. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

The addition of Potassium or Sodium Chloride to mannitol 10% may cause precipitation of mannitol.

6.3 Shelf life

Unopened: 500 ml containers: is 3 years

After opening, with or without additives:

Chemical and Physical stability of any additive at the pH of Mannitol solution (4.5 to 7.0) in the container should be established prior to use.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

The bags, known as pouch is composed of PVC. The bags are overwrapped with a nylon composed of polypropylene which serves only to provide physical protection to the bag.

Bag sizes: 500 ml.

Outer carton contents:

20 bags of 500ml

6.6 Special precautions for disposal and other handling

Use administration sets with a final in-line filter because of the potential for mannitol crystals to form. For instructions on precautions to be taken before administration in case of crystallization of the medicinal product see section 4.2.

Additives may be introduced before infusion or during infusion through the re-sealable medication port.

Thorough and careful aseptic mixing of any additive is mandatory. Solutions containing additives should be used immediately and not stored.

Before adding a medicinal product, verify it is soluble in water at the pH of mannitol solution.

Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

Opening

- Remove the container from the over pouch just before use.
- Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution, as sterility may be impaired.
- Check solution for limpidity and absence of foreign matter. If solution is not clear or contains foreign matter, discard the solution.

Preparation for administration

Use sterile material for preparation and administration.

- Suspend container from eyelet support. Remove plastic protector from outlet port at bottom of container:
 - grip the small wing on the neck of the port with one hand
 - grip the large wing on the cap with the other hand and twist,
 - the cap will pop off.
- Use an aseptic method to set up the infusion. Attach administration set. Refer to complete directions accompanying set.

Techniques for injection of additive medicinal products

Warning: Additives may be incompatible. Check additive compatibility with both the solution and container prior to use.

To add medicinal products before administration:

- Disinfect medication site. Using syringe with 19 to 22 gauge needle, puncture resalable medication port and inject.

Mix solution and medication thoroughly. For high-density medication such as potassium chloride, tap the ports gently while ports are upright and mix.

Caution: Do not store bags containing added medications.

To add medicinal products during administration:

1. Close clamp on the set
2. Disinfect medication site.
3. Using syringe with 19 to 22 gauge needle, puncture resalable medication port and inject.
4. Remove container from intravenous pole and/or turn to an upright position.
5. Evacuate both ports by tapping gently while the container is in an upright position.
6. Mix solution and medication thoroughly.
7. Return container to in use position, re-open the clamp and continue administration.

7. APPLICANT/MANUFACTURER

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