1. Name of the medicinal product

ABTOL, Mannitol intravenous infusion BP 20% w/v

2. Qualitative and quantitative composition

Each 1ml of solution contains 200mg of Mannitol B.P.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Intravenous solution for infusion.

4. Clinical particulars

4.1 Therapeutic indications

Mannitol Intravenous infusion 20% w/v 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

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, Elderly and Children over 6 years:

Acute renal failure

The general dose range is 50 to 200 g mannitol in a 24-hour period (250 to 1000 ml/day), with a dosage limit of 50g mannitol (250ml) on any one occasion. In most instances adequate response will be achieved at a dosage of 50g to 100g mannitol/day (250 to 500 ml/day). The normal infusion rate is 30 to 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 per hour, with a maximum dose of 200 g/24h.

An infusion of 50 to I 00gm of Mannitol may be given during cardiovascular and other types of surgery as an aid in preventing acute renal failure. The concentration and volume to be administered will depend upon the fluid requirement of the patient.

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 1 ml/kg body weight (bw) (200 mg mannitol/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 2 g/kg bw (7.5 to IO 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 induction of forced diuresis in the adjunctive treatment of severe drug intoxications, the dose of mannitol should be adjusted to maintain urinary output of at least I 00ml/hour and positive fluid balance of 1-2 liters. An initial loading dose of approximately 125 ml may be given.

Pediatric Population:

In renal insufficiency, the test dose should be I ml/kg bw (200 mg mannitol/kg bw) over 3-5 minutes. The treatment dose ranges from 0.5 to 1.5 g/kg bw (2.5 ml to7.5 ml/kg bw). This dose may be repeated once or twice, after an interval of 4 to 8 hours, if necessary.

For increased intracranial and intraocular pressure, 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 mannitol in a 24-hour period (250 to 1000 ml/day), with a dosage limit of 50 g mannitol (250 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.

Administration:

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

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Use only if the solution is clear, without visible particles and the seal is intact.

Confirm the integrity of the bottle. Use only if the container is undamaged. Administer immediately following insertion of the infusion set.

Monitoring:

To identify excessive fluid and electrolyte shifts and for early detection of renal, cardiac and other complications, it is essential to monitor:

- serum osmolarity,
- serum electrolytes and acid base balance,
- for signs of dehydration or hypervolemia and
- renal, cardiac and pulmonary function.

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

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 70°C, with agitation. Solutions should not be heated in water or in a microwave oven due to the potential for product contamination or damage. Allow the solution to cool to room or body temperature before reinspection for crystals and use.

4.3 Contraindications

Mannitol Intravenous Infusion 20% is contra-indicated in patients presenting with:

- Pre-existing plasma hyperosmolarity
- 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
- Failure to respond to test dosing -see section 4.2
- Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia.

4.4 Special warnings and special precautions for use

WARNINGS

Hypersensitivity

Anaphylactic/anaphylactoid reactions, including anaphylaxis, as well as other hypersensitivity/infusion reactions have been reported with mannitol. Fatal outcome has been reported.

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, 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
- Hyponatremia 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 preexisting compromised blood brain barrier, the risk of increasing cerebral edema (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 pretreatment renal function who received large intravenous doses of mannitol.

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.

Mannitol should be administered with caution to patients with impaired renal function.

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 hypervolemia

Evaluate cardiovascular status of the patient prior to mannitol administration.

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

- Hypematremia, dehydration and hemoconcentration (resulting from excessive water loss)
- Hyponatremia (resulting from increased sodium excretion during mannitol-induced osmotic diuresis or from the shift of intracellular fluid into extracellular spaces)

  Hyponatremia can lead to headache, nausea, seizures, lethargy, coma, cerebral edema, and death. Acute symptomatic Hyponatremic encephalopathy is considered a medical emergency.

  The risk for developing hyponatremia 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 hyponatremia is increased, for example,

  -In pediatric patients (<16 years of age)

  -In women (in particular, premenopausal women)

  -In patients with hypoxemia

  -In patients with underlying central nervous system disease.
- Hypokalemia
- Hyperkalemia
- Other electrolytes imbalances
- Metabolic acidosis
- Metabolic alkalosis

  By sustaining diuresis, mannitol administration may obscure and intensify inadequate hydration or hypovolemia.

  <u>Infusion reactions</u>

  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 and bullous eruptions) when associated with extravasation.

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).

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

In patients with shock and renal dysfunction, mannitol should not be administered until volume (fluid; blood) and electrolytes have been replaced.

PRECAUTIONS

Volume and electrolyte replacement before use

Mannitol should not be administered in patients with hypovolemic shock or renal dysfunction until volume and electrolytes have been restored.

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 70°C, with agitation.

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 m which mannitol is initially oxidized to an aldehyde.

Pediatric use

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

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 connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container.
- Pressurizing 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.

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

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

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

The cardiovascular status of the patient should be carefully evaluated before rapidly administering Mannitol 20% Solution for Infusion since sudden expansion of the extracellular fluid may lead to sudden congestive heart failure.

Shift of sodium-free intracellular fluid into the extra cellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatremia.

Sodium may be lost in the urine. Mannitol may obscure and intensify inadequate hydration and hypovolemia.

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

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

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.

In cooler temperatures mannitol may form crystals. Storing it at a temperature of 20° to 30° will minimize the deposition of crystals. Redissolve any crystallized mannitol

by moderately warming the product in a water bath, gently agitating the solution periodically.

ENSURE THAT THE SOLUTION IS COOLED TO 37° C BEFORE INFUSION

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 2.6.

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.

Inhibition Effect

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

Although an interaction in humans is unlikely, patients receiving concomitant cyclosporine 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.

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).

4.6 Fertility, pregnancy and lactation

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

There are no relevant published data from animal studies with respect to mannitol's effect on pregnancy and/or embryo/fetal 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

There is no information on the effects of mannitol on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

The following adverse reactions have been reported in post-marketing experience

System or Organ Class	**Adverse Drug Reaction**
Immune System disorder	Allergic reaction Anaphylactic reaction including anaphylactic shock
Metabolism and Nutritional disorders	Fluid and Electrolyte imbalance - Dehydration - Oedema - Metabolic acidosis
Nervous system disorders	Headache Dizziness Rebound intracranial pressure increase CNS toxicity manifested by: - Convulsions - Coma - Confusion - Lethargy
Eye disorder	Blurred vision
Cardiac disorders	Cardiac arrhythmia Congestive heart failure
Vascular disorders	Hypotension Pulmonary oedema
Respiratory, thoracic and mediastinal disorders	Rhinitis
Gastrointestinal disorders	Mouth dry
Skin and subcutaneous tissue disorders	Skin necrosis Urticaria
Musculoskeletal and connective tissue disorders	Cramps
Renal and urinary disorders	Excessive dieresis Nephrosis osmotic Urinary retention Acute renal failure Azotemia Anuria Oliguria Polyuria
General disorders and	Chills

administration site conditions	Chest pain (angina-like chest pain) Fever Asthenia Malaise Infusion site reactions including: - infusion thrombophlebitis - infusion site inflammation - infusion site pain - infusion site rash - infusion site erythema - infusion site pruritus Compartment syndrome (associated with extravasation and swelling at the injection site)

- *It can be manifested with skin, gastrointestinal, and severe circulatory (hypotension), and respiratory manifestations
- (e.g., dyspnea). Other hypersensitivity/infusion reactions include hypertension, pyrexia, chills, sweating, cough, musculoskeletal stiffness and myalgia, urticaria/rash, pruritus, generalized pain, discomfort, nausea, vomiting, and headache.
- **including hypervoalaemia, peripheral oedema, dehydration, hyponatraemia, hypernatraemia, hyperkalaemia, hypokalaemia.

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. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

Prolonged administration or rapid infusion of large volumes of hyperosmotic solutions may result 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.

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: B05BCO l

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 I 0% 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 are 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 humor and thereby reduces intraocular pressure.

5.2 Pharmacokinetic properties

When administered intravenously, mannitol is eliminated largely unmetabolized through the glomeruli. It is freely filtered by the glomeruli, with less than I 0% 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

Not available.

6. Pharmaceutical particulars

6.1 List of excipients

- Water for injection

6.2 Incompatibilities

Mannitol 20% Solution for Infusion should not be administered simultaneously with, before, or after administration of blood through the same infusion equipment, due to risk of pseudo agglutination.

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

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

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).

As a guide, 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 20% may cause precipitation of mannitol.

6.3 Shelf life

36 months from date of manufacture.

Once opened, use immediately.

6.4 Special precautions for storage

Store below 30°C, but do not freeze.

6.5 Nature and contents of container

The product is a colorless or almost colorless solution.

Bottle sizes: 500/100 mL.

The bottles are made from Low Density Polyethylene plastic; the bottles are then overwrapped with a protective plastic pouch composed of polyamide/polypropylene which are ultimately packed in individual baby cartons.

6.6 Special precautions for disposal and other handling

Use as directed by physician. Keep out of reach of children.

Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following insertion of the infusion set.

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

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

Medicinal products may be introduced before infusion or during infusion through the injection site.

Mannitol solutions may crystallize when exposed to low temperature. Inspect for crystals prior to administration. If crystals are visible, re-dissolve by warming the solution up to a maximum of 70°C, with agitation. Solutions should not be heated in water or in a microwave oven due to the potential for product contamination or damage. Allow the solution to cool to room or body temperature before reinspection for crystals and use. Discard after single use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturer

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8. Marketing authorization number(s)

N/A

9. Date of first authorization/renewal of the authorization

N/A

10. Date of revision of the text

N/A