PRESCRIBING INFORMATION

OSMITROL INJECTION 10%
Mannitol Injection USP 10%
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Solution for Infusion
Osmotic Diuretics

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Prescribing Information
Osmitrol Injection

For Therapeutic Use Only

Summary Product Information
Osmitrol Injection is a sterile, nonpyrogenic solution of mannitol USP in a single dose container for intravenous administration. It contains no antimicrobial agents. Mannitol is a six carbon sugar alcohol prepared commercially by the reduction of dextrose. Although virtually inert metabolically in humans, it occurs naturally in fruits and vegetables. Mannitol is an obligatory osmotic diuretic. The pH is adjusted with sodium hydroxide or hydrochloric acid. Composition, osmolarity, and pH are shown in Table 1

Table 1

	Mannitol USP g/l	APPROX OSMOLARITY (mOsmol/L)	APPROX pH	VOLUME
Osmitrol Injection 10%	100	549	5.5	1000 mL
Osmitrol Injection 20%	200	1100	5.5	500 mL

The VIAFLEX plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Action and Clinical Pharmacology
Osmitrol Injection is one of the nonelectrolyte, obligatory, osmotic diuretics. It is freely filterable at the renal glomerulus, only poorly reabsorbed by the renal tubule, not secreted by the tubule, and is pharmacologically inert. Mannitol, when administered intravenously, exerts its osmotic effect as a solute of relatively small molecular size being largely confined to the extracellular space. Only relatively small amounts of the dose administered is metabolized. Mannitol is readily diffused through the glomerulus of the kidney over a wide range of normal and impaired kidney function. In this fashion, approximately 80% of a 100 gram dose of mannitol will appear in the urine in three hours with lesser amounts thereafter. Even at peak concentrations, mannitol will exhibit less than 10% of tubular reabsorption and is not secreted by tubular cells. Mannitol will hinder tubular reabsorption of water and enhance excretion of sodium and chloride by elevating the osmolarity of the glomerular filtrate.
This increase in extracellular osmolarity effected by the intravenous administration of mannitol will induce the movement of intracellular water to the extracellular and vascular spaces. This action underlies the role of mannitol in reducing intracranial pressure, intracranial edema, and elevated intraocular pressure.

Indications and Clinical Use
Osmitrol Injection 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 edema by reducing brain mass;
- The reduction of elevated intraocular pressure when the pressure cannot be lowered by other means, and
- Promoting the urinary excretion of toxic substances.

Contraindications
Osmitrol Injection is contraindicated in patients with:
- Known hypersensitivity to mannitol
- Well established anuria due to severe renal disease
- Failure to respond to test dosing (see Dosage and Administration)
- Pre-existing severe pulmonary vascular congestion or pulmonary edema

- Active intracranial bleeding except during craniotomy
- Severe dehydration
- Pre-existing plasma hyperosmolarity
- Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia,
- Progressive heart failure or pulmonary congestion after institution of mannitol therapy.

Osmitrol Injection is also contraindicated in patients with a known hypersensitivity to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Prescribing Information.

Warnings and Precautions

General

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.

Hypersensitivity/Infusion reactions
Anaphylactic/anaphylactoid reactions, including anaphylaxis, as well as other hypersensitivity/infusion reactions have been reported with mannitol. Fatal outcome has been reported (see Adverse Reactions section).

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 Post-marketing Adverse Reactions section).

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.

Neurologic
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.

Renal
Reversible, acute oligoanuric renal failure has occurred in patients with normal pretreatment renal function who received large intravenous doses of mannitol. Osmotic nephrosis, a reversible vacuolization of the tubules of unknown clinical significance, may proceed to severe irreversible nephrosis, so that the renal function must be closely monitored during mannitol infusion.

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 (see also Dosage and administration).

If urine output continues to decline during mannitol infusion, the patient's clinical status should be closely reviewed and mannitol infusion suspended if necessary.

In patients with severe impairment of renal function, a test dose should be utilized (see Dosage and Administration). A second test dose may be tried if there is an inadequate response, but no more than two test doses should be attempted.

Cardiovascular
The cardiovascular status of the patient should be carefully evaluated before rapidly administering mannitol since sudden expansion of the extracellular fluid may lead to fulminating congestive heart failure.

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
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:

- Hypernatremia, 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

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.

Serum sodium and potassium should be carefully monitored during mannitol administration.

With continued administration of mannitol, loss of water in excess of electrolytes can cause hypernatremia. Electrolyte measurements, including sodium and potassium, are therefore, of vital importance in monitoring the infusion of mannitol.

Shift of sodium free intracellular fluid into the extracellular compartment following mannitol infusion may lower serum sodium concentration and aggravate preexisting hyponatremia.

Hematologic
Mannitol should not be given concomitantly with blood because it may cause agglutination and crenation of blood cells. It is essential that blood be given simultaneously, at least 20 mEq of sodium chloride should be added to each liter of mannitol solution to avoid pseudoagglutination.

The obligatory diuretic response following rapid infusion of Osmitrol injection 20% may further aggravate preexisting hemoconcentration.

Special Populations
Pregnant Women
Animal reproduction studies have not been conducted with mannitol. It is also not known whether mannitol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Mannitol should be given to a pregnant woman only if clearly needed.

Nursing Women
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mannitol is administered to a nursing woman.

Pediatrics
Safety and effectiveness in children below the age of 12 have not been established.
Dosage requirements for patients 12 years of age and under have not been established.

Geriatrics
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.

Monitoring and Laboratory Tests
Although blood levels of mannitol can be measured, there is little if any clinical virtue in doing so. The appropriate monitoring of blood levels of sodium and potassium; degree of hemoconcentration or hemodilution, if any; indices of renal, cardiac and pulmonary function are paramount in avoiding excessive fluid and electrolyte shifts. The routine features of physical examination and clinical chemistries suffice in achieving an adequate degree of appropriate patient 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.

Laboratory test Interference:
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.

Adverse Reactions

The list of adverse reactions in this Prescribing Information is based on post-marketing reports (see below).

Post-Market Adverse Drug Reactions:
The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then, where feasible, by Preferred Term in order of severity.

IMMUNE SYSTEM DISORDERS: Anaphylactic/anaphylactoid reactions, including anaphylaxis, 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

METABOLISM AND NUTRITION DISORDERS: Fluid and electrolyte imbalances, including hypervolemia, peripheral edema, dehydration, hyponatremia, hypernatremia, hyperkalemia, hypokalemia, metabolic acidosis

NERVOUS SYSTEM DISORDERS: CNS toxicity manifested by, e.g. Coma, Convulsion, Confusion, Lethargy, Rebound increase in intracranial pressure, Dizziness

CARDIAC DISORDERS: Congestive cardiac failure, Palpitations

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Pulmonary edema

GASTROINTESTINAL DISORDERS: Thirst, Dry mouth

RENAL AND URINARY DISORDERS: Renal failure acute, Osmotic nephrosis, Renal impairment, Azotemia, Anuria, Hematuria, Oliguria, Polyuria

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Asthenia, Malaise; Infusion site reactions, including infusion site phlebitis, infusion site inflammation, infusion site pain, infusion site rash, infusion site erythema, infusion site pruritus; Compartment syndrome, and swelling at the injection site associated with extravasation (see also infusion site reaction statement in Section Warnings and Precautions for Use)

OTHER REACTIONS: Severe anaphylaxis with cardiac arrest, and fatal outcome

Adverse reactions which may occur because of the solution or the technique of administration include, rhinitis, dizziness, tachycardia, and angina-like chest pains.

Failure to recognize severe impairment of renal function with the high likelihood of nondiuretic response can lead to aggravated dehydration of tissues and increased vascular fluid load. Induced diuresis in the presence of preexisting hemoconcentration and preexisting deficiency of water and electrolytes can lead to serious imbalances. Expansion of the extracellular space can aggravate cardiac decompensation or induce it in the presence of latent heart failure. Pulmonary congestion or edema can be seriously aggravated with the expansion of the extracellular and therefore intravascular fluid load.

Hemodilution and dilution of the extracellular fluid space by osmotic shift of water can induce or aggravate preexisting hyponatremia.
If unrecognized, such fluid and/or electrolyte shift can produce the reported adverse reactions of pulmonary congestion, acidosis, electrolyte loss, dryness of mouth, thirst, edema, headache, blurred vision, convulsions and congestive cardiac failure.

Drug Interactions

Neurotoxic agents
Concomitant use of neurotoxic agents (e.g. aminoglycoside) and mannitol may potentiate the toxicity of neurotoxic agents. (see also Warnings and Precautions for Use).

Nephrotoxic agents
Concomitant administration of nephrotoxic drugs (e.g., cyclosporine, aminoglycoside) increases the risk of renal failure following administration of mannitol.

Other diuretics
Other diuretics may potentiate the effects of mannitol.

Agents affected by electrolyte imbalances
The development of electrolyte imbalances (e.g., hyperkalemia, hypokalemia) 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).

Renally-eliminated agents
Mannitol therapy may increase the elimination, and decrease the effectiveness of treatment with, agents that undergo significant renal elimination, such as lithium.

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

Dosage and Administration

Osmitrol Injection, must be administered only by intravenous infusion, using sterile and nonpyrogenic equipment. The total dosage, concentration, and rate of administration should be governed by the nature and severity of the condition being treated, fluid requirement, and urinary output. The usual adult dosage ranges from 20 to 100 g in a 24 hour period, but in most instances an adequate response will be achieved at a dosage of approximately 50 to 100 g in a 24 hour period. The rate of administration is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour. This outline of administration and dosage is only a general guide to therapy. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact. Confirm the integrity of the bag. Use only if the bag is not damaged. Hyperosmolar mannitol solutions may cause vein damage. Administer through a large central vein. Check product's osmilarity before administration.Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L. Administration of substantially hypertonic solutions (> 600 mOsmol/L) may cause vein damage.

When exposed to low temperatures, solutions of mannitol may crystallize. Concentrations greater than 10% have a greater tendency to crystallization. Inspect for crystals prior to administration. If crystals are visible, redissolve by warming the solution up to 70ºC, 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 temperature before reinspection for crystals. Administer intravenously using an administration set with a sterile final in-line filter because of the potential for mannitol crystals to form.

Test Dose:
In patients with oliguria or those believed to have inadequate renal function, a test dose of mannitol should be given prior to instituting mannitol therapy.

A test dose may be approximately 0.2 g mannitol per kg body weight infused over 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.

In adult patients, such a test should produce a urine flow of at least 30 to 50 mL/hour. If urine flow does not increase, a second test dose may be given.

If an adequate response to a second test dose is not attained, treatment with mannitol should be discontinued and the patient reassessed as, e.g., established renal failure may be present.

Prevention of Acute Renal Failure (Oliguria):
When used during cardiovascular and other types of surgery, 50 to 100g of mannitol as a 10% solution may be given.
The concentration will depend upon the fluid requirements of the patient.

Treatment of Oliguria:
The usual dose for treatment of oliguria is 100 g administered as a 20% solution.
Reduction of Intraocular Pressure: A dose of 1.5 to 2.0 g/kg as a 20% solution (7.5 to 10 mL/kg) may be given over a period as short as 30 minutes in order to obtain a prompt and maximal effect. When used preoperatively the dose should be given one to one and one-half hours before surgery to achieve maximal reduction of intraocular pressure before operation.

Reduction of Intracranial Pressure:
Usually a maximum reduction in intracranial pressure in adults can be achieved with a dose of 0.25 g/kg given not more frequently than every six to eight hours. An osmotic gradient between the blood and cerebrospinal fluid of approximately 10 mOsmol will yield a satisfactory reduction in intracranial pressure.

Adjunctive Therapy for Intoxications:
As an agent to promote diuresis in intoxications, Osmitrol Injection 10% or 20% is indicated. The concentration will depend upon the fluid requirement and urinary output of the patient.
Measurement of glomerular filtration rate by creatinine clearance may be useful for determination of dosage. These injections are intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.
The use of supplemental additive medication is not recommended.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre

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

In case of suspected overdose, treatment with mannitol must be stopped immediately. Management of overdose is symptomatic and supportive, with appropriate monitoring (see Warnings and Precautions for Use).

Mannitol is dialyzable (hemodialysis and peritoneal dialysis), hemodialysis may speed mannitol elimination.

Storage and Stability
Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Store at 15ºC to 25°C.

Dosage Forms, Composition and Packaging
See Summary Product Information, Table 1 which shows the available sizes in Viaflex plastic (polyvinyl chloride) containers. See Table 1 for sizes, composition, osmolarity, approx. pH and volume of Osmitrol Injection.

Directions for Use of VIAFLEX Plastic Containers
Warning: Do not use plastic container in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open
Tear overwrap down side at slit and remove solution container. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Preparation for Administration
1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

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