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OSMITROL Injection (Mannitol Injection, USP) in AVIVA Plastic Container

For Therapeutic Use Only

Description

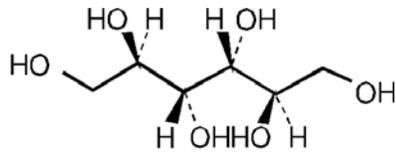
Osmitrol Injection (Mannitol Injection, USP) is a sterile, nonpyrogenic solution of Mannitol, USP in a single dose container for intravenous administration. It contains no antimicrobial agents. Mannitol** is a six carbon sugar alcohol prepared commercially by the reduction of dextrose. Although virtually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

Table 1	Composition			
	Size (mL)	**Mannitol, USP (g/L)	*Osmolarity (mOsmol/L) (calc)	pH
5% OSMITROL Injection (5% Mannitol Injection, USP)	1000	50	274	5.5 (4.5 TO 7.0)
10% OSMITROL Injection (10% Mannitol Injection, USP)	500	100	549	5.5 (4.5 TO 7.0)
	1000			
15% OSMITROL Injection (15% Mannitol Injection, USP)	500	150	823	5.5 (4.5 TO 7.0)
20% OSMITROL Injection (20% Mannitol Injection, USP)	250	200	1098	5.5 (4.5 TO 7.0)
	500			

*Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L.
Administration of substantially hypertonic solutions (≥ 600 mOsmol/L) may cause vein damage.

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Mannitol

The flexible container is made with non-latex plastic materials specially designed for a wide range of parenteral drugs including those requiring delivery in containers made of polyolefins or polypropylene. For example, the AVIVA container system is compatible with and appropriate for use in the admixture and administration of paclitaxel. In addition, the AVIVA container system is compatible with and appropriate for use in the admixture and administration of all drugs deemed compatible with existing polyvinyl chloride container systems. The solution contact materials do not contain PVC, DEHP, or other plasticizers.

The suitability of the container materials has been established through biological evaluations, which have shown the container passes Class VI U.S. Pharmacopeia (USP) testing for plastic containers. These tests confirm the biological safety of the container system.

The flexible container is a closed system, and air is prefilled in the container to facilitate drainage. The container does not require entry of external air during administration.

The container has two ports: one is the administration outlet port for the attachment of an intravenous administration set and the other port has a medication site for addition of supplemental medication (See Directions for Use). The primary function of the overwrap is to protect the container from the physical environment.

Clinical Pharmacology

Osmitrol Injection (Mannitol Injection, USP) 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

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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 Usage

Osmitrol Injection (Mannitol Injection, USP) 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 (Mannitol Injection, USP) is contraindicated in patients with:

Well established anuria due to severe renal disease, severe pulmonary congestion or frank pulmonary edema, active intracranial bleeding except during craniotomy, severe dehydration, Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia, and progressive heart failure or pulmonary congestion after institution of mannitol therapy.

Warnings

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.

The obligatory diuretic response following rapid infusion of 15% or 20% mannitol injection may further aggravate preexisting hemoconcentration. Excessive loss of water and electrolytes may lead to serious imbalances. Serum sodium and potassium should be carefully monitored during mannitol 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. Accumulation of mannitol may result in overexpansion of the extracellular fluid which may intensify existing or latent congestive heart failure.

Excessive loss of water and electrolytes may lead to serious imbalances. 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

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infusion 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.

Precautions

General

Do not connect flexible plastic containers of intravenous solutions in series, i.e., do not piggyback connections. Such use could result in air embolism due to residual air being drawn from one container before administration of the fluid from a secondary container is completed.

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 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.

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

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

Electrolyte free mannitol should not be given conjointly with blood. If 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.

When exposed to low temperatures, solutions of mannitol may crystallize. Concentrations greater than 15% have a greater tendency to crystallization. Inspect for crystals prior to administration. If crystals are visible, redissolve by warming the solution up to 70°C, with agitation. Allow the solution to cool to room temperature before reinspection for crystals. Administer intravenously using sterile, **filter-type** administration set.

Laboratory Tests

Although blood levels of mannitol can be measured, there is little if any clinical virtue in doing so.

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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.

Drug Interaction

Studies have not been conducted to evaluate drug/drug or drug/food interactions with Osmitol Injection (Mannitol Injection, USP).

Carcinogenesis, mutagenesis, impairment of fertility

Studies with Osmitol Injection (Mannitol Injection, USP) have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category C. 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.

Labor and Delivery

Studies have not been conducted to evaluate the effects of Osmitol Injection (Mannitol Injection, USP) on labor and delivery. Caution should be exercised when administering this drug during labor and delivery.

Nursing Mothers

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.

Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

Usage in Children

Dosage requirements for patients 12 years of age and under have not been established.

Geriatric Use

Clinical studies of Osmitol Injection (Mannitol Injection, USP) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in the responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely

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to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Adverse Reactions

Extensive use of mannitol over the last several decades has produced recorded adverse events, in a variety of clinical settings, that are isolated or idiosyncratic in nature. None of these adverse reactions have occurred with any great frequency nor with any security in attributing them to mannitol.

The inability to clearly exclude the drug related nature of such events in these isolated reports prompts the necessity to list the reactions that have been observed in patients during or following mannitol infusion. In this fashion, patients have exhibited nausea, vomiting, rhinitis, local pain, skin necrosis and thrombophlebitis at the site of infection, chills, dizziness, urticaria, hypotension, hypertension, tachycardia, fever and angina-like chest pains.

Of far greater clinical significance is a variety of events that are related to inappropriate recognition and monitoring of fluid shifts. These are not intrinsic adverse reactions to the drug but the consequence of manipulating osmolarity by any agency in a therapeutically inappropriate manner. Failure to recognize severe impairment of renal function with the high likelihood of non-diuretic 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.

These are not truly adverse reactions to the drug and can be appropriately prevented by evaluation of degree of renal failure with a test dose response to mannitol when indicated; evaluation of hypervolemia and hypovolemia; sodium and potassium levels; hemodilution or hemoconcentration; and evaluation of renal, cardiac and pulmonary function at the onset of therapy.

Dosage and Administration

Osmitol Injection (Mannitol Injection, USP) should be administered only by intravenous infusion. 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

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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. Use of a final filter is recommended during administration of all parenteral solutions, where possible. Do not administer unless solution is clear and seal is intact.

Test Dose: A test dose of mannitol should be given prior to instituting Osmitol Injection (Mannitol Injection, USP) therapy for patients with marked oliguria, or those believed to have inadequate renal function. Such a test dose may be approximately 0.2 g/kg body weight (about 75 mL of a 20% solution or 100 mL of a 15% solution) infused in a period of three to five minutes to 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 there is an inadequate response, the patient should be reevaluated.

Prevention of Acute Renal Failure (Oliguria): When used during cardiovascular and other types of surgery, 50 to 100 g of mannitol as a 5, 10, or 15% 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 15 or 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) or as a 15% solution (10 to 13 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 mOsmols will yield a satisfactory reduction in intracranial pressure.

Adjunctive Therapy for Intoxications: As an agent to promote diuresis in intoxications, 5%, 10%, 15% or 20% mannitol 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.

All injections in AVIVA containers are intended for intravenous administration using sterile equipment.

The use of supplemental additive medication is not recommended.

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How Supplied

Osmitrol Injection (Mannitol Injection, USP) in AVIVA plastic containers is available as follows:

Code	Size (mL)	NDC	Product Name
6E5604	1000	0338-6300-04	5% Osmitrol Injection (5% Mannitol Injection, USP)
6E5613	500	0338-6301-03	10% Osmitrol Injection
6E5614	1000	0338-6301-04	(10% Mannitol Injection, USP)
6E5623	500	0338-6302-03	15% Osmitrol Injection (15% Mannitol Injection, USP)
6E5632	250	0338-6303-02	20% Osmitrol Injection
6E5633	500	0338-6303-03	(20% Osmitrol Injection)

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (25°C); brief exposure up to 40°C does not adversely affect the product.

Directions for Use of AVIVA Plastic Container

To Open

Tear overwrap down side at slit and remove solution container. Moisture and some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Preparation for Administration

Caution: Do not use plastic containers in series connections.

Caution: Use only with a non-vented set or a vented set with the vent closed.

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

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* Bar Code Position Only

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