

**MANNITOL I.V.**  
**MANNITOL Injection, USP**  
**Flexible Plastic Container**  
**Fliptop Vial**                      R<sub>x</sub> only

**DESCRIPTION**

Mannitol I.V. (Mannitol Injection, USP) is a sterile, nonpyrogenic solution of mannitol in water for injection available in concentrations of 5%, 10%, 15%, 20% in flexible plastic containers and 25% in a fliptop vial for administration by intravenous infusion only.

The content and characteristics of the available concentrations are as follows:

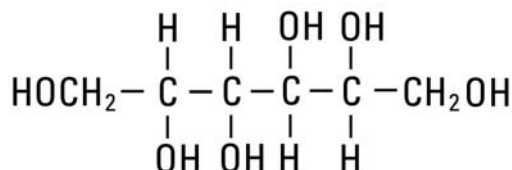
Conc. (%)	g/100 mL	mOsmol/liter (calc.)	pH*
5	5	274	6.3 (4.5 to 7.0)
10	10	549	6.3 (4.5 to 7.0)
15	15	823	6.3 (4.5 to 7.0)
20	20	1098	6.3 (4.5 to 7.0)
25	25	1372	5.9 (4.5 to 7.0)

\*Concentrations up to 20% may contain sodium bicarbonate for pH adjustment; the 25% concentration may contain sodium bicarbonate and/or hydrochloric acid for pH adjustment.

The solutions contain no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and each is intended only as a single-dose injection. When smaller doses are required the unused portion should be discarded.

Mannitol Injection, USP is a parenteral obligatory osmotic diuretic.

Mannitol, USP is chemically designated D-mannitol (C<sub>6</sub>H<sub>14</sub>O<sub>6</sub>), a white crystalline powder or free-flowing granules freely soluble in water. It has the following structural formula:



Water for Injection, USP is chemically designated H<sub>2</sub>O.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap, but not in amounts sufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period.

**CLINICAL PHARMACOLOGY**

When administered intravenously mannitol is confined to the extracellular space, only slightly metabolized and rapidly excreted by the kidney. Approximately 80% of a 100 g dose appears in the urine in 3 hours. The drug is freely filtered by the glomeruli with less than 10% tubular reabsorption; it is not secreted by tubular cells. Mannitol induces diuresis by elevating the osmolarity of the glomerular filtrate and thereby hindering tubular reabsorption of water. Excretion of sodium and chloride is also enhanced.

## **INDICATIONS AND USAGE**

Mannitol I.V. (Mannitol Injection, USP) is indicated for the following purposes in adults and pediatric patients.

### **Therapeutic Use**

1. Promotion of diuresis in the prevention or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established.
2. Reduction of intracranial pressure and brain mass.
3. Reduction of high intraocular pressure when the pressure cannot be lowered by other means.
4. Promotion of urinary excretion of toxic materials.

### **Diagnostic Use**

Measurement of glomerular filtration rate.

## **CONTRAINDICATIONS**

1. Well established anuria due to severe renal disease.
2. Severe pulmonary congestion or frank pulmonary edema.
3. Active intracranial bleeding except during craniotomy.
4. Severe dehydration.
5. Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia.
6. Progressive heart failure or pulmonary congestion after institution of mannitol therapy.
7. Do not administer to patients with a known hypersensitivity to mannitol.

## **WARNINGS**

1. 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.
2. The obligatory diuretic response following rapid infusion of 25% mannitol may further aggravate pre-existing hemoconcentration. Excessive loss of water and electrolytes may lead to serious imbalances. Serum sodium and potassium should be carefully monitored during mannitol administration.
3. 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.
4. 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 infusion of mannitol.
5. Osmotic nephrosis, a reversible vacuolization of the tubules of no known clinical significance, may proceed to severe irreversible nephrosis, so that the renal function must be closely monitored during mannitol infusion.
6. Mannitol injection may increase cerebral blood flow and the risk of postoperative bleeding in neurosurgical patients.
7. For intravenous use only. Do not administer intramuscularly or subcutaneously. Never add mannitol in whole blood for transfusion.
8. Mannitol may increase the cerebral blood flow and worsen intracranial hypertension in children who develop a generalized cerebral hyperemia during the first 24 to 48 hours post injury.

## **PRECAUTIONS**

1. 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.
2. Shift of sodium-free intracellular fluid into the extracellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatremia.
3. By sustaining diuresis, mannitol administration may obscure and intensify inadequate hydration or hypovolemia.
4. Electrolyte-free mannitol solutions 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.
5. When exposed to low temperatures, solutions of mannitol may crystallize. If crystals are observed, the container should be warmed to redissolve, then cooled to body temperature before administering. See NOTE under HOW SUPPLIED. When infusing 20% or 25% mannitol concentrations, the administration set should include a filter. Do not infuse mannitol solution if crystals are present.
6. Do not administer unless solution is clear and container is undamaged. Discard unused portion. Do not administer Mannitol 25% if the fliptop vial seal is not intact.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies with solutions from flexible plastic containers have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

*Pregnancy Category C.* Animal reproduction studies have not been conducted with mannitol injection. It is also not known whether mannitol injection can cause fetal harm when given to a pregnant woman or can affect reproduction. Mannitol injection should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** Caution should be exercised when solutions from flexible plastic containers are administered to a nursing mother.

**Pediatric Use:** See DOSAGE AND ADMINISTRATION sections. Safety and effectiveness of solutions from flexible plastic containers in pediatric patients have not been well established.

## **ADVERSE REACTIONS**

Adverse reactions more commonly reported during or after the infusion of mannitol include: Pulmonary congestion, fluid and electrolyte imbalance, acidosis, electrolyte loss, dryness of mouth, thirst, marked diuresis, urinary retention, edema, headache, blurred vision, convulsions, nausea, vomiting, rhinitis, arm pain, skin necrosis, thrombophlebitis, chills, dizziness, urticaria, dehydration, hypotension, tachycardia, fever and angina-like chest pains.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

## **OVERDOSAGE**

Too rapid infusion of large amounts of mannitol will cause a shift of intracellular water into the extracellular compartment resulting in cellular dehydration and overexpansion of the intravascular space with hyponatremia, congestive heart failure and pulmonary edema. Repeated doses should not be given to patients with persistent oliguria as this can produce a hyperosmolar state and

precipitate congestive heart failure and pulmonary edema due to volume overload. Dosage must be carefully monitored and adjusted in accordance with the clinical situation to avoid the consequences of overdosage. See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.

### **DOSAGE AND ADMINISTRATION**

Mannitol I.V. (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 50 to 200 g in a 24-hour period, but in most instances an adequate response will be achieved at a dosage of approximately 100 g/24 hours. The rate of administration is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hr. The total dose should be adjusted according to the clinical response and adverse events (see WARNINGS).

*Test Dose:* A test dose of mannitol should be given prior to instituting Mannitol I.V. therapy for patients with marked oliguria or those believed to have inadequate renal function. In adults the dose is 0.2 g/kg body weight. In pediatric patients the dose is 0.2 g/kg body weight or 6 g/m<sup>2</sup> body surface area. The infusion is given as a 15% to 25% solution over a period of 3 to 5 minutes to produce a urine flow of at least 30 to 50 mL/hour. If urine flow does not increase, a second dose may be given; but if there is inadequate response, the patient should be re-evaluated.

*Prevention of Acute Renal Failure (Oliguria):* When used during cardiovascular or other types of surgery, 50 to 100 g of mannitol as a 5%, 10%, or 15% solution may be given. The concentration will depend on the fluid requirements of the patient.

*Treatment of Oliguria:* The usual dose to promote diuresis in oliguric patients: Adults, 300 to 400 mg/kg of body weight (21 to 28 g for a 70 kg patient) or up to 100 g of solution, given as a single dose (often in conjunction with furosemide); pediatric patients, 0.25 to 2 g/kg body weight or 60 g/m<sup>2</sup> body surface area as a 15% to 20% solution over a period of 2 to 6 hours. Doses should not be repeated in patients with persistent oliguria.

*Reduction of Intracranial Pressure and Brain Mass:* In adults a dose of 0.25 to 2 g/kg body weight as a 15% to 25% solution administered over a period of 30 to 60 minutes; pediatric patients 1 to 2 g/kg body weight or 30 to 60 g/m<sup>2</sup> body surface area over a period of 30 to 60 minutes. In small or debilitated patients, a dose of 500 mg/kg may be sufficient. Careful evaluation must be made of the circulatory and renal reserve prior to and during administration of mannitol at the higher doses and rapid infusion rates. Careful attention must be paid to fluid and electrolyte balance, body weight, and total input and output before and after infusion of mannitol. Evidence of reduced cerebral spinal fluid pressure must be observed within 15 minutes after starting infusion.

*Reduction of Intraocular Pressure:* In adults a dose of 0.25 to 2 g/kg body weight as a 15% to 25% solution administered over a period of 30 to 60 minutes; pediatric patients 1 to 2 g/kg body weight or 30 to 60 g/m<sup>2</sup> body surface area over a period of 30 to 60 minutes. In small or debilitated patients, a dose of 500 mg/kg may be sufficient. 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.

*Adjunctive Therapy for Intoxications:* As an agent to promote urinary excretion of toxic substances: Adults may receive a 5% to 25% solution for as long as indicated if urinary output remains high; pediatric patients may receive 2 g/kg of body weight of a 5% or 10% solution. The concentration will depend upon the fluid requirement and urinary output of the patient. If benefits are not observed after 200 g of mannitol are administered, discontinue the mannitol therapy.

Intravenous water and electrolytes must be given to match the loss of these substances in the urine, sweat and expired air.

*Measurement of Glomerular Filtration Rate (GFR):* 100 mL of a 20% solution (20 g) should be diluted with 180 mL of sodium chloride injection (normal saline) or 200 mL of a 10% solution (20 g) should be diluted with 80 mL of sodium chloride injection (normal saline). The resulting 280 mL of 7.2% solution is infused at a rate of 20 mL per minute. The urine is collected by catheter for a specific period of time and analyzed for mannitol excreted in mg per minute. A blood sample is drawn at the start and at the end of the time period and the concentration of mannitol determined in mg/mL of plasma. GFR is the number of mL of plasma that must have been filtered to account for the amount excreted per minute in the urine. Normal clearance rates are approximately 125 mL/minute for men; 116 mL/minute for women.

### **Drug Interactions**

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives to the flexible container, use aseptic technique, mix thoroughly and do not store.

Do not place 25% Mannitol Injection, USP in polyvinylchloride bags; a white flocculent precipitate may form from contact with PVC surfaces. Parenteral drug products should be inspected visually for particulate matter and discoloration; whenever container and solution permit. See PRECAUTIONS.

### **INSTRUCTIONS FOR USE - Flexible Container**

#### **To Open**

Tear outer wrap at notch and remove solution container. If supplemental medication is desired, follow directions below before preparing for administration. 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.

#### **To Add Medication**

1. Prepare additive port.
2. Using aseptic technique and an additive delivery needle of appropriate length, puncture resealable additive port at target area, inner diaphragm and inject. Withdraw needle after injecting medication.
3. The additive port may be protected by covering with an additive cap.
4. Mix container contents thoroughly.

#### **Preparation for Administration**

##### **(Use aseptic technique)**

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

**WARNING: Do not use flexible container in series connections.**

### **INSTRUCTIONS FOR USE - Fliptop Vial**

Remove cover and cleanse stopper with antiseptic before use.

**HOW SUPPLIED**

Mannitol I.V. (Mannitol Injection, USP) is supplied in single-dose containers as follows:

<b>List No.</b>	<b>Conc. %</b>	<b>Size (mL)</b>
7712	5	1000 Flexible Container
7713	10	1000 Flexible Container
7714	15	500 Flexible Container
7715	20	250 Flexible Container
		500 Flexible Container
4031	25	50 Fliptop Vial

NOTE: Crystals may form in mannitol solutions especially if the solutions are chilled. To dissolve crystals in the flexible container, warm the unit to 70°C with agitation. Heat solution by using a dry-heat cabinet with overwrap intact. The use of a water bath is not recommended. To dissolve the crystals in the fliptop vial, warm the bottle in hot water at 80°C and periodically shake vigorously. 25% Mannitol Injection, USP may be autoclaved at 121°C for 20 minutes at 15 psi. Remove cover from fliptop vial and cleanse stopper with antiseptic before use. Cool to body temperature or less before administering. When infusing 20% or 25% mannitol concentrations, the administration set should include a filter.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

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