MANNITOL (Systemic)

Category

Diuretic; antiglaucoma agent (systemic); antihemolytic.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Acute renal failure, oliguric phase (prophylaxis and treatment)¾Mannitol, administered intravenously, is indicated to promote diuresis in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established 1.

Edema, cerebral (treatment) 1 or

Intracranial pressure, elevated (treatment) 1¾Mannitol, administered intravenously, is indicated to reduce intracranial pressure and treat cerebral edema by reducing brain mass 1.

Intraocular pressure, elevated (treatment) 1¾Mannitol, administered intravenously, is indicated to reduce elevated intraocular pressure after other methods have failed or in preparation for intraocular surgery. 1, 3, 4, 5, 6

Toxicity, nonspecific (treatment)¾Mannitol, administered intravenously, is indicated to promote urinary excretion of and prevent renal damage due to toxic substances (for example, salicylates, barbiturates, bromides, lithium). 1, 3, 4, 5, 6

Hemolysis (prophylaxis)¾Mannitol, when used as an irrigating solution, is indicated to prevent hemolysis and hemoglobin buildup during transurethral prostatic resection or other transurethral surgical procedures. 3, 4, 5, 6 [It has also been used to prevent hemolysis during cardiopulmonary bypass procedures.] *

Unaccepted

Mannitol has been used to measure glomerular filtration rate (GFR) in acute oliguria but has generally been replaced by more accurate tests.

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Mannitol is an osmotic diuretic that is metabolically inert in humans and occurs naturally, as a sugar, in fruits and vegetables 1.

Osmotic agent (systemic)¾

Mannitol elevates blood plasma osmolality, resulting in enhanced flow of water from tissues, including the brain and cerebrospinal fluid, into interstitial fluid and plasma. As a result, cerebral edema, elevated intracranial pressure, and cerebrospinal fluid volume and pressure may be reduced.

Diuretic¾

Induces diuresis because mannitol is not reabsorbed in the renal tubule, thereby increasing the osmolality of the glomerular filtrate, facilitating excretion of water, and inhibiting the renal tubular reabsorption of sodium, chloride, and other solutes 1.

It may, therefore, promote the urinary excretion of toxic materials and protect against nephrotoxicity by preventing the concentration of toxic substances in the tubular fluid.

Antiglaucoma agent¾

Elevates blood plasma osmolarity, resulting in enhanced flow of water from the eye into plasma and a consequent reduction in intraocular pressure.

Antihemolytic¾

When used as an irrigating solution in transurethral prostatic resection, dilute solutions of mannitol may minimize the hemolytic effect of water used alone. The entrance of hemolyzed blood into the circulation and the resultant hemoglobinemia may also be reduced.

Diagnostic aid (renal function)¾

Mannitol is freely filtered by the glomeruli with less than 10% tubular reabsorption. Therefore, its urinary excretion rate may serve as a measurement of glomerular filtration rate (GFR).

Precautions to Consider

Carcinogenicity

An early study with 1%, 5%, and 10% mannitol given for 94 weeks to Wistar rats found a low incidence of benign thymomas in females. However, a subsequent lifetime study at similar doses in Sprague-Dawley, Fischer, and Wistar rats found no evidence of carcinogenicity. 1

Mutagenicity

In vivo and in vitro mutagenicity studies were negative.

Pregnancy/Reproduction

Pregnancy¾Adequate and well-controlled studies have not been done in humans.
Studies in mice, rats, and rabbits at oral doses up to 1600 mg per kg of body weight (mg/kg) did not find adverse effects on the fetus. 1, 3

FDA Pregnancy Category B. 1

Breast-feeding

It is not known whether mannitol is distributed into breast milk. However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of mannitol have not been performed in the pediatric population. Although mannitol has been used in this population and no pediatrics-specific problems have been documented to date, safety and efficacy have not been established in children younger than 12 years of age 1.

Geriatrics

No information is available on the relationship of age to the effects of mannitol in geriatric patients. However, elderly patients are more likely to have age-related renal function impairment, which may require caution in patients receiving mannitol 2.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Digitalis glycosides

(concurrent use with mannitol may enhance the possibility of digitalis toxicity associated with hypokalemia)

Diuretics, other, including carbonic anhydrase inhibitors

(diuretic and intraocular pressure-reducing effects may be potentiated when these medications are used concurrently with mannitol; dosage adjustments may be necessary)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Phosphate or

Potassium or

Sodium 10

(serum concentrations may be decreased by excessive and prolonged use 8, 9)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Anuria, with well-established acute tubular necrosis due to severe renal disease 3, 4, 5, 6

(if patients do not respond to test dose; accumulation may lead to overexpansion of extracellular fluid and circulatory overload)

>> Dehydration, severe 3, 4, 5, 6

(may be exacerbated by fluid loss caused by mannitol; may result in serious electrolyte imbalances)

>> Heart failure or pulmonary congestion, progressive, after beginning mannitol therapy 1

>> Intracranial bleeding, active, except during craniotomy

(mannitol may increase bleeding by increasing cerebral blood flow 3, 4, 5, 6)

>> Pulmonary congestion or pulmonary edema, severe 3, 4, 5, 6

>> Renal damage or dysfunction, progressive, after beginning mannitol therapy, including worsening oliguria and azotemia 1

Risk-benefit should be considered when the following medical problems exist

>> Cardiopulmonary function impairment, significant

(sudden expansion of extracellular fluid may lead to congestive heart failure 3, 4, 6)

Hyperkalemia 1 or

Hyponatremia 1 or

Hypovolemia 1

(mannitol-induced sudden changes in fluid balance may further aggravate depleted or excessive electrolyte concentrations or fluid volume 1 ; serum sodium concentrations may be further diluted in hyponatremic patients by the shift of sodium-free intracellular fluid into the extracellular compartment 1 ; rapid or prolonged administration of mannitol, causing a loss of water in excess of electrolytes, may result in hypernatremia 1 ; mannitol-induced sustained diuresis may obscure or aggravate hypovolemia 1)

>> Renal function impairment, significant

(accumulation of mannitol may lead to overexpansion of extracellular fluid and circulatory overload 3, 4, 5, 6)

Sensitivity to mannitol

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Blood pressure measurements and

>> Electrolyte measurements, serum, including potassium and sodium, and 3, 4, 5, 6

>> Renal function determinations and 3, 6

>> Urine output determinations 3

(recommended during administration of mannitol, especially with large or repeated doses)

Side/Adverse Effects

Note: The most serious side/adverse effect of mannitol is fluid and electrolyte imbalance. Rapid administration of large doses may lead to accumulation of mannitol, overexpansion of extracellular fluid, dilutional hyponatremia and occasional hyperkalemia, and circulatory overload, especially in patients with acute or chronic renal failure. 12 Inadequate hydration or hypovolemia may be obscured by the diuresis produced by mannitol, which may lead to tissue dehydration, promotion of oliguria, and intensification of pre-existing hemoconcentration. Extravasation of mannitol may result in edema and skin necrosis.
When mannitol is used as an irrigating solution during transurethral prostatectomy, a systemic effect, from the entry of large volumes of mannitol into the systemic circulation, can occur, which can result in a significant alteration of cardiopulmonary and renal dynamics 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Chest pain or fast heartbeat 3, 4, 5, 6; chills or fever 3, 4, 5, 6; difficult urination 3, 4, 5, 6; electrolyte imbalance confusion); irregular heartbeat); muscle cramps or pain); numbness, tingling, pain, or weakness in hands or feet); seizures); trembling); unusual tiredness or weakness); weakness and heaviness of legs); pulmonary congestion coughing); troubled breathing); wheezing); renal failure 13, 14 sudden decrease in amount of urine); swelling of face, feet, or lower legs); skin rash); unusual weight gain); shortness of breath); troubled breathing); wheezing); tightness in chest); increase in blood pressure); unusual thirst); swelling of feet or lower legs 4, 5, 6; thrombophlebitis redness, swelling, or pain at injection site)

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Dryness of mouth or increased thirst 3, 4, 5, 6; headache 3, 4, 5, 6; increased urination 4, 5, 6; nausea or vomiting 3, 4, 5, 6

Incidence less frequent

Blurred vision 3, 4, 5, 6; dizziness 3, 4; skin rash or hives 3, 4, 5, 6

Note: In some cases, headache, nausea or vomiting, blurred vision, and dizziness may be symptoms of subdural or subarachnoid hemorrhage as a result of dehydration of the brain.

General Dosing Information

One gram of mannitol is equivalent to approximately 5.5 milliosmole (mOsm).
The number of mOsm of mannitol per liter of sterile water for injection is as follows:

Mannitol (%)	mOsm/liter (approx)
5	275
10	550
15	825
20	1100
25	1375

Mannitol must be administered by intravenous infusion.

The administration set should include a filter when mannitol solutions with concentrations of 15% or above are infused, since these solutions have a greater tendency to crystallize when exposed to low temperatures.
The total dosage, concentration, and rate of administration should be determined by the nature and severity of the condition being treated, fluid requirement, and urinary output 1.

The rate is usually adjusted to maintain an adequate urine flow (at least 30 to 50 mL per hour) 1.

Mannitol infusion should be discontinued promptly if urine output is low 1.

A test dose of mannitol is recommended prior to therapy in patients with marked oliguria or possible inadequate renal function 1.

The test dose is given as an intravenous infusion, 200 mg per kg of body weight (mg/kg) as a 15 to 25% solution, administered over a period of three to five minutes. 3, 4, 5 In children the dose is 200 mg/kg

or 6 grams per square meter of body surface area as a 15 to 25% solution, administered over a period of three to five minutes. If urine flow does not increase to at least 30 to 50 mL per hour for two to three hours after this or a second test dose, mannitol should be withheld until the patient is re-evaluated. 3, 4, 5

If renal failure, heart failure, or pulmonary congestion progresses after starting mannitol therapy, mannitol should be discontinued 1.

Alkalinization of the urine with sodium bicarbonate may be necessary to aid in treatment of salicylate or barbiturate poisonings.

Parenteral Dosage Forms

MANNITOL INJECTION USP

Note:

As a general guide to therapy, the usual adult dose ranges from 50 to 200 grams in a twenty-four hour period, but in most cases an adequate response will be achieved at a usual dosage of approximately 100 grams in twenty-four hours 1.

Usual adult dose

Acute renal failure (oliguria), prophylaxis¾
During surgery, immediately postoperatively, or following trauma: Intravenous infusion, 50 to 100 grams as a 5 to 25% solution, the concentration and amount depending upon the fluid requirements of the patient 1.

Following suspected or actual hemolytic transfusion reactions to provoke diuresis: Intravenous infusion, 20 grams, over a period of five minutes 1.

If diuresis does not occur, the 20-gram dose may be repeated 1.

If urine flow is adequate (30 to 50 mL per hour), intravenous fluids containing not more than 50 to 75 milliequivalents (mEq) of sodium per liter should be given in sufficient volume to match the desired urine flow (100 mL per hour) until the patient can take fluids orally 1.

Acute renal failure (oliguria), treatment¾
Intravenous infusion, 50 to 100 grams as a 15 to 25% solution 1.

Cerebral edema or
Elevated intracranial pressure or
Elevated intraocular pressure¾
Intravenous infusion, 0.25 10 to 2 grams per kg of body weight as a 15 to 25% solution, administered over a period of thirty to sixty minutes. 3, 4, 5, 6 The patient's fluid and electrolyte balance, body weight, and total input and output should be closely monitored before and after infusion of mannitol 1.

Evidence of reduced cerebral-spinal fluid pressure may be observed within fifteen minutes after starting the infusion 1.

Maximal reduction of intraocular pressure occurs thirty to sixty minutes after the injection 1.

When used preoperatively, the dose should be given sixty to ninety minutes before surgery to achieve maximum reduction of pressure before operation 17.

Note: In small or debilitated patients, a dose of 500 mg per kg of body weight may be sufficient.
Toxicity, nonspecific (to promote urinary excretion of toxic substances)¾
Intravenous infusion, as a 5 to 25% solution (the concentration dependent upon the patient's fluid requirement and urinary output), as long as indicated if the level of urinary output remains high 1.

Intravenous water and electrolytes must be given to replace the loss of these substances in the urine, sweat, and expired air 1.

If benefits are not observed after administering 200 grams, mannitol should be discontinued 1.

Antihemolytic (urologic irrigation)¾
Mannitol may be used as a 2.5% irrigating solution for the bladder during transurethral prostatic resection or other transurethral surgical procedures. 3

Usual adult prescribing limits

6 grams per kg of body weight per twenty-four hours.

Usual pediatric dose

Diuretic¾
Intravenous infusion, 0.25 to 10 2 grams per kg of body weight or 60 grams per square meter of body surface area as a 15 to 20% solution, administered over a period of two to six hours.
Cerebral edema or
Elevated intracranial pressure or
Elevated intraocular pressure¾
Intravenous infusion, 1 to 2 grams per kg of body weight or 30 to 60 grams per square meter of body surface area as a 15 to 20% solution, administered over a period of thirty to sixty minutes.

Note: In small or debilitated patients, a dose of 500 mg per kg of body weight may be sufficient.
Toxicity, nonspecific¾
Intravenous infusion, up to 2 grams per kg of body weight or 60 grams per square meter of body surface area as a 5 to 10% solution.

Strength(s) usually available

U.S.¾5% (Rx)[Osmitrol] [Generic]

10% (Rx)[Osmitrol] [Generic]

15% (Rx)[Osmitrol] [Generic]

20% (Rx)[Osmitrol] [Generic]

25% (Rx)[Osmitrol] [Generic]

Canada¾5% (Rx)[Osmitrol 18]

10% (Rx)[Osmitrol 18]

15% (Rx)[Osmitrol 18]

20% (Rx)[Osmitrol 18]

25% (Rx) [Generic] 18

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Preparation of dosage form:

To prepare a 2.5% irrigating solution, add the contents of two 50-mL ampuls of 25% Mannitol Injection USP to 900 mL of sterile water for injection. 4

Stability:

Solutions of mannitol may crystallize, especially if chilled. To dissolve crystals, see manufacturer's package insert for directions. If all crystals cannot be completely dissolved, the solution should not be used. 3, 4

The contents of opened containers should be used promptly. Unused contents should be discarded. 3, 4

Incompatibilities:

Electrolyte-free mannitol solutions should not be given conjointly with blood. If blood must be administered simultaneously with mannitol, at least 20 mEq (mmol) of sodium chloride should be added to each liter of mannitol solution to prevent pseudoagglutination.