OSMITROL INTRAVENOUS INFUSION
(MANNITOL INTRAVENOUS INFUSION, BP)

Name of the Medicine

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion, BP) contains Mannitol. It contains no antimicrobial agents.

Description

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion, BP) is a sterile, nonpyrogenic solution of Mannitol BP, in a single dose container for intravenous administration. Mannitol $C_6H_{14}O_6$ is a six carbon sugar alcohol prepared commercially by the reduction of glucose. The molecular weight for Mannitol is 182.2, CAS Number 69-65-8. 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 and hydrochloric acid. Composition, osmolarity and pH are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Size</th>
<th>Composition (Mannitol BP)</th>
<th>*Osmolarity mOsmol/L</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Osmitrol IV Infusion (10% Mannitol IV Infusion BP)</td>
<td>1000 mL, 100 g/1000 mL</td>
<td>550</td>
<td>5.5 (4.5 to 7.0)</td>
</tr>
<tr>
<td>20% Osmitrol IV Infusion. (20% Mannitol IV Infusion. BP)</td>
<td>500 mL, 100g/500 mL</td>
<td>1100</td>
<td>5.0 (4.5 to 7.0)</td>
</tr>
</tbody>
</table>

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

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 sufficient 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 tissue culture toxicity studies.
Pharmacology

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion BP) is one of the non-electrolyte, obligatory, osmotic diuretics. It is freely filterable at the renal glomerulus, is poorly reabsorbed by the renal tubule, is 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 are metabolised. 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 the tubular cells. Mannitol will hinder tubular reabsorption of water and enhance excretion of sodium and chloride by elevating the osmolarity of the glomerular filtrate.

The increase in extracellular osmolarity affected by the intravenous administration of Mannitol will induce the movement of intracellular water to the extracellular and vascular spaces. The action underlies the role of Mannitol in reducing intracranial pressure, intracranial oedema, and reducing elevated intraocular pressure.

Indications

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion, BP), can be used in:

- 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 elevated intraocular pressure when the pressure cannot be lowered by other means;
- The reduction of intracranial pressure and treatment of cerebral oedema by reducing brain mass and;
- Promoting the urinary excretion of toxic substances.

Contraindications

Osmitrol Intravenous Infusion (Mannitol BP) is contraindicated in patients with:

- Hypersensitivity to Mannitol
- Pre-existing plasma hyperosmolarity
- Severe heart failure
- Disturbance of the blood-brain barrier
- Well established anuria due to severe renal disease
- No response to test dose
• Severe pulmonary congestion or frank pulmonary oedema
• 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.

Precautions

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

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

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic drugs, are at increased risk of renal failure following administration of Osmitrol. Serum osmolarity, urine flow and renal function should be monitored particularly closely.

The acid base, renal function and serum osmolarity must be monitored carefully when Osmitrol is used. Should patient serum osmolarity increase during treatment, the effects of Osmitrol on diuresis and reduction of intracranial and intraocular pressures may be impaired.

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

Osmitrol is hypertonic. Hypertonic solutions should be administered via a large peripheral and preferably central vein. Rapid infusion in peripheral veins may be harmful.

The obligatory diuretic response following rapid infusion of a 20% Mannitol Intravenous Infusion may further aggravate pre-existing haemoconcentration. Excessive loss of water and electrolytes, may lead to serious imbalances. Serum sodium and potassium should be carefully monitored during Mannitol administration.

A rebound increase in intracranial pressure may occur approximately 12 hours after the use of Mannitol for the reduction of intracranial pressure.

The use of Mannitol in acute traumatic brain injury and acute stroke is not recommended. This is based on 2 Systematic Reviews that indicate the potential for harm and lack of sufficient data for a definitive assessment of the risk or benefit for using Mannitol in these two clinical conditions.
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 infusion of Mannitol.

Osmotic nephrosis, a reversible vacuolisation 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.

The use of supplemental additive medication is not recommended.

The cardiovascular status of the patient should be carefully evaluated before rapidly administrating 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 pre-existing hyponatremia.

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

Electrolyte and Mannitol Intravenous Infusions should be not given co-jointly with blood. If it is essential that blood be given simultaneously, at least 20mEq of sodium chloride should be added to each litre of Mannitol solution to avoid pseudoagglutination.

There may be potential incompatibility with additives which include the risk of precipitation if potassium or sodium chloride is added to Mannitol. Also some antibiotics including cefepime, imipenem or cilastatin may be incompatible with Mannitol.

When exposed to low temperatures, solutions of Mannitol may crystalise. Concentrations of 20% have a greater tendency to crystallisation. Inspect for crystals prior to administration. If crystals are visible, redisolve 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 a sterile, filter-type set.

**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 haemoconcentration and haemodilution, if any, indices of renal, cardiac and pulmonary
function are paramount in avoiding excess fluid and electrolyte shifts. The routine features of physical examination and clinical chemistries suffice in achieving an adequate degree of appropriate patient monitoring.

**Use in Pregnancy (Category B2)**

**Teratogenic Effects**

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

**Use in Lactation**

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when Mannitol is administered to a nursing woman.

**Usage in Children**

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

Safety and effectiveness in this population have not been established.

**Usage in Geriatrics**

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 in 24-hour period), with a dosage limit of 50 g on any one occasion. Since incipient renal insufficiency may be present, caution should be used when reviewing patient’s status prior to dose selection.

**Interactions with other Medicines**

Potentiation effects – concurrent use of other diuretics may potentiate the effects of Mannitol and dose adjustments may be required.

Inhibition effects – concomitant use of Mannitol impairs the response to lithium and methotrexate due to the increases in urinary excretion.

Cumulative nephrotoxicity – patients receiving concomitant cyclosporin should be closely monitored for signs of nephrotoxicity.

Other potential interactions – caution regarding concomitant use with aminoglycosides (potentiation of ototoxic effects), depolarising neuromuscular blocking agents
(enhancement of their effects), oral anti-coagulants (reduce their effects by increasing concentration of clotting factors secondary to dehydration), and digoxin (digoxin toxicity if hypokalaemia follows Mannitol treatment).

**Adverse Effects**

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 or with any security in attributing them to Mannitol.

The inability to clearly exclude the medicine related nature of such events in these isolated reports prompts the necessity to list the reactions that have been observed in patients during the following Mannitol infusions.

Immediate reactions: can be noted, very rarely and in the same manner than with all Osmitrol solutions. (In these cases the infusion must be discontinued).

**Gastrointestinal Disorder:**
- Nausea
- Vomiting

**Hypersensitivity reactions:**
- Local pain
- Skin necrosis
- Thrombophlebitis at the site if Intravenous Infusion
- Rhinitis
- Angioedema
- Allergic reaction
- Anaphylactic shock

**Neurological reactions:**
- Chills
- Dizziness
- Urticaria
- Fever
- Headache
- Blurred vision
- Intracranial pressure increase

**Circulatory effects:**
- Hypotension
- Hypertension
- Tachycardia
- Cardiac arrhythmia
- Angina-like chest pain
- Pulmonary congestion Oedema
- Convulsions
- Congestive cardiac failure
Renal effects: Nephrosis osmotic  
Alveolar nephrosis  
Large doses of Mannitol have been known to cause acute renal failure even in patients with satisfactory pre-treatment renal function  
Excessive diuresis  
Urinary retention

Blood disturbances:  
Acidosis  
Fluid and Electrolyte imbalance

Metabolic/Nutritional disorder:  
Dehydration  
Oedema  
Cramps  
Thirst  
Dryness of mouth

Of far greater clinical significance are a variety of events that are related to inappropriate recognition and monitoring of fluid shifts. These are not intrinsic adverse reactions to the medicine but the consequence of manipulating osmolarity by an agency in a therapeutically inappropriate manner. Failure to recognise 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 pre-existing haemoconcentration and pre-existing 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 oedema can be seriously aggravated with the expansion of the extracellular fluid space by osmotic shift of water can induce or aggravate pre-existing hyponatraemia.

These are not truly adverse reactions to the medicine 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; haemodilution or haemoconcentration and evaluation of renal, cardiac and pulmonary function at the onset of therapy.

**Dosage and Administration**

**Dosage**

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion BP) 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. There should be a dosage limit of 50 g of Osmitrol on any one occasion. 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 medicine products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

Test Dose: A test dose of Mannitol should be given prior to instituting Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion, BP) 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) 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 re-evaluated.

Prevention of Acute Renal Failure (oliguria): When used during cardiovascular and other types of surgery, 50 to 100 g of Mannitol as a 10% or 20% 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 maximum effect. When used pre-operatively the dose should be given one to one and a half hours before surgery to achieve maximum 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 per kg given not more frequently than every six to eight hours. An osmotic gradient between the blood and cerebrospinal fluid of approximately 10 mOsm/l per litre will yield a satisfactory reduction in intracranial pressure.

Adjunctive Therapy for Intoxication: As an agent to promote diuresis in intoxications, 10% 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 creatine clearance may be useful for determination of dosage.

All IV Infusions in Viaflex containers are intended for intravenous administration using sterile equipment.
Directions for use

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. Caution should be used due to the possibility of air embolism with the pressurisation of intravenous solutions in flexible plastic containers and with the use of a vented intravenous administration set with the vent open.

To open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilisation 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 the inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Preparation for Administration

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

Overdosage

In case of suspected overdose, treatment with Osmitrol 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 electrolyte balance. Haemodialysis may be useful.

If poisoning does occur, contact the nearest Poisons Information Centre telephone number 13 11 26.

Presentation

Osmitrol Intravenous Infusion (Mannitol Intravenous Infusion, BP) in Viaflex plastic containers is available as follows:

<table>
<thead>
<tr>
<th>Code</th>
<th>Size (mL)</th>
<th>ARTG No</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHB3026</td>
<td>1000</td>
<td>AUST R 19479</td>
<td>10% Osmitrol IV Infusion (10% Mannitol IV Infusion, BP)</td>
</tr>
<tr>
<td>AHB3025</td>
<td>500</td>
<td>AUST R 19496</td>
<td>20% Osmitrol IV Infusion (20% Mannitol IV Infusion, BP)</td>
</tr>
</tbody>
</table>
Exposure of pharmaceutical products to heat should be minimised. Avoid excessive heat. It is recommended the product should be stored below 30°C; brief exposure up to 40°C does not adversely affect the product.

**Storage Condition**
The product should be stored below 30°C.

**Name and Address of the Sponsor**
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

**Poison Schedule**
Not scheduled

**Approved by the TGA: 21 March 2007**

**Date of most recent amendment: 12 July 2011**