SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MANNITOL / VIOSER SOLUTION FOR INFUSION 20%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution contains Mannitol 200 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless aqueous solution, free from visible particles.
Theoretical osmolarity: 1098 mOsm/l
pH: 4.5-7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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.

4.2 Posology and method of administration

Mannitol / VIOSER solution for infusion 20% 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 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.

Test Dose:
A test dose of mannitol should be given prior to instituting Mannitol / VIOSER solution for infusion 20% 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 mOsmol 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.

4.3 Contraindications

Mannitol / VIOSER solution for infusion 20% is contra-indicated in patients presenting with:
- Hypersensitivity to mannitol
- Severe pulmonary congestion or pulmonary oedema
- Irreversible anuria
- Recent intracranial bleeding, except during craniotomy
- Heart failure
- Loss of water and electrolytes
- Chronic kidney disease

4.4 Special warnings and precautions for use

Caution in administration in renal failure and pregnancy. Prior to administration, careful assessment of the condition of the cardiovascular system is required, followed by continuous monitoring of diuresis and serum electrolytes.

Administration should not be repeated to patients who remain anuric following administration of a test dose.

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic drugs, are at increased risk of renal failure following administration of mannitol. Serum osmolal gap and renal function should be closely monitored and necessary action initiated, should signs of worsening renal function appear.

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

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

The cardiovascular status of the patient should be carefully evaluated before rapidly administering mannitol, since sudden expansion of the extracellular fluid may cause sudden 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 hyponatraemia. Sodium may be lost in the urine. Mannitol may obscure and intensify inadequate hydration and hypovolaemia.

Urinary output, fluid balance, central venous pressure and electrolyte balance (in particular serum sodium and potassium levels) should be carefully monitored.

Accumulation of mannitol may result if urine output continues to decline during administration and this may intensify existing or latent congestive heart failure.

Precautions during administration

Avoid extravasation (risk of local necrosis).
Mannitol in the 20% solution may crystallise.
To dissolve crystals, the bottle is heated in hot water and shaken vigorously.
The solution should be infused at body temperature (see section 6.6).
It is recommended to use a haemofilter when infusing 20% mannitol solution to prevent potential infusion of mannitol microcrystals.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of other diuretics may potentiate the effects of mannitol and dose adjustments may be required.

Mannitol increases the elimination of medicinal products excreted through urine (e.g. lithium and methotrexate) and, therefore, concomitant use of mannitol may impair the response to these medicinal products.

Patients receiving concomitant cyclosporine should be closely monitored for signs of nephrotoxicity.

Other potential interactions are with aminoglycosides (potentiation of their ototoxic effects by mannitol), depolarising neuromuscular blocking drugs (enhancement of their effects by mannitol), oral anticoagulants (mannitol may reduce their effects by increasing the concentration of clotting factors secondary to dehydration) and digitalis (if hypokalaemia

follows mannitol treatment, there is a risk of digitalis toxicity), although there is limited evidence of such interactions occurring in humans.

It should not be administered concomitantly with blood.

If it is essential that blood be given simultaneously, at least 20 milliequivalents of sodium chloride should be added to each litre of mannitol solution to avoid pseudoagglutination.

4.6 Fertility, pregnancy and lactation

There are no adequate published data from the use of mannitol in pregnant women. There are no adequate published data, from animal studies, with respect to mannitol's effect on pregnancy and/or foetal development and/or parturition and/or postnatal development. Mannitol should not be administered during pregnancy, unless absolutely necessary.
There is no information on excretion of mannitol in breast milk. Mannitol should not be administered during lactation.
Intense removal of water from the body is expected to disrupt the normal production of milk during breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions are classified as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Frequency	**System Organ Class**	**Adverse Reactions**
Uncommon (≥1/1,000 to <1/100)	Metabolism and nutrition disorders	Fluid and electrolyte disorders
	Vascular disorders	Hypotension
	Vascular disorders	Thrombophlebitis
Rare (≥1/10,000 to <1/1,000)	Immune system disorders	Allergic reaction*
		Anaphylactic shock*
	Metabolism and nutrition disorders	Dehydration
		Oedema
	Nervous system disorders	Headache
		Convulsions
		Dizziness
		Rebound intracranial pressure increase
	Eye disorders	Blurred vision
	Cardiac disorders	Cardiac arrhythmia
	Vascular disorders	Hypertension
		Pulmonary oedema
	Gastrointestinal disorders	Dry mouth
		Thirst
		Nausea
		Vomiting
	Skin and subcutaneous tissue disorders	Skin necrosis
		Urticaria
	Musculoskeletal and connective tissue disorders	Cramps

	Renal and urinary disorders	Excessive diuresis
		Osmotic nephrosis
		Urinary retention
	General disorders and administration site conditions	Chest pain (angina-like chest pain)
		Fever
Very rare (<1/10,000)	Cardiac disorders	Congestive heart failure
	Renal and urinary disorders	Acute renal failure
Not known (cannot be estimated from the available data)	Nervous system disorders	Convulsions
		Painful arm
	Cardiac disorders	Pulmonary congestion
		Metabolic acidosis
		Tachycardia
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Gastrointestinal disorders	Diarrhoea
	Musculoskeletal and connective tissue disorders	Chills
	General disorders and administration site conditions	Infusion site thrombosis/phlebitis
* It can be manifested with skin, gastrointestinal, and severe circulatory (hypotension) and respiratory manifestations (e.g. dyspnea). Other hypersensitivity/infusion reactions include hypertension, pyrexia, chills, sweating, cough, shivering and myalgia, urticaria/rash, pruritus, generalized pain, discomfort, nausea, vomiting and headache.		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

In case of suspected overdose, treatment with mannitol 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, unconsciousness and coma may follow.

Treatment: The infusion is stopped immediately and supportive measures are applied to correct water and electrolyte disorders. Haemodialysis helps to eliminate mannitol and reduce the increased osmotic pressure of the serum.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically active diuretics,
ATC code: "B05BC01"

Mannitol/VIOSER solution for infusion 20% belongs to the osmotically active diuretics. Mannitol, a virtually non-metabolizable carbohydrate, is rapidly eliminated by the renal

glomerulus and is not reabsorbed by the renal tubules, entraining water and sodium. The distribution of mannitol is confined to the extracellular fluid volume.

5.2 Pharmacokinetic properties

The volume of mannitol distribution corresponds to the volume of the extracellular fluid. Mannitol is rapidly excreted by the kidneys along with water and sodium.
The elimination half-life in adults is approximately 2 hours, longer where renal failure is present. 80% of an intravenous dose is excreted unchanged within 3 hours.

5.3 Preclinical safety data

The intravenous administration of Mannitol/VIOSER hypertonic solution for infusion 20% temporarily reduces intracranial and intraocular pressure, due to water shifting from the cells into the extracellular space.

The Mannitol/VIOSER hypertonic solution for infusion 20% is preferred over hypertonic solutions of sodium chloride, dextrose, sorbitol, sucrose and urea because it has fewer side effects.
However, reckless administration of mannitol may cause some complications. Thus e.g. administration of large doses of mannitol to heart patients may cause fulminant heart failure due to rapid increase of the extracellular fluid volume. On the contrary, forced osmotic diuresis can lead to significant loss of sodium, potassium and water.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

Mannitol / VIOSER solution for infusion 20% should not be administered simultaneously with, before, or after administration of blood through the same infusion equipment, due to risk of pseudoagglutination.
Concomitant blood transfusion requires concomitant administration of sodium chloride (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Incompatibility of the medicinal product to be added to the mannitol solution must be assessed before addition.

Before adding a medicinal product, verify it is soluble and stable in water at the pH of the mannitol solution (4.5 to 7.0).

As an example, cefepime, imipenem, cilastin and filgrastim are incompatible with mannitol solutions. The addition of potassium chloride or sodium chloride to 20% mannitol solutions may cause precipitation of mannitol.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials. After opening the container, use the solution immediately.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Polyethylene plastic bottle of 250 ml.

6.6 Special precautions for disposal and other handling

Do not use the product after its expiry date. Any unused solution should be disposed of.
Do not use the content if:
a) it is not clear, it is not without visible particles and the bottle is not intact
b) disinfection with 70% alcohol has not taken place at
- the surface around the site of insertion of the set
- any other perforation site.
In cooler temperatures mannitol may form crystals.
The crystals can be redissolved before use by warming in a water bath (at a temperature of approximately 60°C), agitating the solution vigorously periodically. Cool the solution to body temperature (37°C) before infusion.

7. MANUFACTURER

VIOSER S.A. PARENTERAL SOLUTIONS INDUSTRY,
9th Km National Road Trikala-Larisa, Taxiarches Trikala, 42100, Greece.

8. MARKETING AUTHORISATION HOLDER

ELDAN ELECTRONIC INSTRUMENTS CO LTD,
Hashiloah 6, POB 7641, Petach Tiqva 4917001, Israel.

9. MARKETING AUTHORISATION NUMBER

172-38-36484-99

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