SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DEXTROSE 4.3 % AND 0.18 % SODIUM CHLORIDE VIOSER, SOLUTION FOR INFUSION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1000ml solution contains:
Sodium Chloride: 1.8 g
Dextrose anhydrous: 43.0 g

Each ml contains 1.8 mg sodium chloride and 43 mg dextrose anhydrous.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear and colorless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dextrose 4.3 % and 0.18 % sodium chloride Vioser solution is used in the following indications:

Dehydration treatment due to a moderated loss of sodium and chloride (vomiting, diarrhoea, renal disorders, overuse of diuretics) in cases where a source of energy is required (particularly starvation).

Paediatric Population:

This product should only be used in paediatric specialist settings (such as renal, hepatic and cardiac units, high dependency units and intensive care units) for intravenous fluid therapy requiring the use of dextrose 4.3 % and 0.18 % sodium chloride to maintain fluid and electrolyte balance.

4.2 Posology and method of administration

The choice of the specific sodium chloride and dextrose (glucose) concentration, dosage, volume, rate and duration of administration depends on the age, weight, clinical condition of the patient and concomitant therapy. It should be determined by a physician. For patients with electrolyte and glucose abnormalities and for paediatric patients, consult a physician experienced in intravenous fluid therapy.

Fluid balance, serum glucose, serum sodium and other electrolytes should be monitored before and during administration, especially in patients with increased non-osmotic vasopressin release (syndrome of inappropriate antidiuretic hormone secretion, SIADH) and in patients co-medicated with vasopressin agonist drugs due to the risk of hyponatraemia. Monitoring of serum sodium is particularly important for

physiologically hypotonic fluids. Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution may become extremely hypotonic after administration due to dextrose (glucose) metabolisation in the body (see sections 4.4, 4.5 and 4.8).

Rapid correction of hyponatraemia and hypernatraemia is potentially dangerous (risk of serious neurologic complications).

Electrolyte supplementation may be indicated according to the clinical needs of the patient.

Adults, older patients and adolescents (age 12 years and over):

The recommended dosage is 500 ml to 3 L/24h

Administration rate

The infusion rate is usually 40 ml/kg/24h and should not exceed the patient's dextrose (glucose) oxidation capacities to avoid hyperglycaemia. Therefore, the maximum acute administration rate is 5 mg/kg/min.

Paediatric Population

Use of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v should be restricted to specialist paediatric settings such as renal, hepatic and cardiac units, high dependency units and intensive care units.

The dosage varies with weight:

0-10 kg body weight:	100 ml/kg/24h
10-20 kg body weight:	1000 ml + (50 ml/kg over 10 kg)/24h
> 20 kg body weight:	1500 ml + (20 ml/kg over 20 kg)/24h

The administration rate varies with weight:

0-10 kg body weight:	6-8 ml/kg/h
10-20 kg body weight:	4-6 ml/kg/h
> 20 kg body weight:	2-4 ml/kg/h

The infusion rate should not exceed the patient's dextrose (glucose) oxidation capacities to avoid hyperglycaemia. Therefore, the maximum acute administration rate is 10-18 mg/kg/min, depending on the total body mass.

For all patients, a gradual increase of flow rate should be considered when starting administration of dextrose (glucose) containing products.

Method of administration

The administration is performed by intravenous infusion.
Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution is hypotonic and hyperosmolar, due to the dextrose (glucose) content.

Precautions to be taken before manipulating or administering the product

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear, and the seal is intact. Administer immediately following the insertion of infusion set.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution to prevent air entering the system.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

Additives may be introduced before or during infusion through the injection site. When additive is used, verify isotonicity prior to parenteral administration. Hyperosmolar solutions may cause venous irritation and phlebitis. Thus, any hyperosmolar solution is recommended to be administered through a large central vein, for rapid dilution of the hyperosmotic solution.

For further information on the product with additives, please see sections 6.2, 6.3 and 6.6.

4.3 Contraindications

The solution is contraindicated in patients presenting with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Extracellular hyperhydration or hypervolaemia
- Fluid and sodium retention
- Severe renal insufficiency (with oliguria/anuria)
- Uncompensated cardiac failure
- Hyponatraemia or hypochloraemia
- General oedema and ascitic cirrhosis
- Clinically significant hyperglycaemia.

The solution is also contraindicated in case of uncompensated diabetes, other known dextrose (glucose) intolerances (such as metabolic stress situations), hyperosmolar coma or hyperlactataemia.

Paediatric Population

This product should not be used in children except in paediatric specialist settings (such as renal, hepatic and cardiac units, high dependency units and intensive care units) under expert medical supervision.

4.4 Special warnings and precautions for use

Dextrose (glucose) intravenous infusions are usually isotonic solutions. In the body, however, dextrose (glucose) containing fluids can become extremely physiologically hypotonic due to rapid dextrose (glucose) metabolization (see section 4.2).

Depending on the tonicity of the solution, the volume and rate of infusion and depending on a patient's underlying clinical condition and capability to metabolize dextrose (glucose), intravenous administration of dextrose (glucose) can cause electrolyte disturbances, most importantly hypo- or hyperosmotic hyponatraemia.

Hyponatraemia

The infusion of solutions with sodium concentrations <0.9% may result in hyponatraemia. Close clinical monitoring maybe warranted.

Patients with non-osmotic vasopressin release (e.g., in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (brain oedema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with brain oedema are at particular risk of severe, irreversible and life-threatening brain injury.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g., meningitis, intracranial bleeding, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

Sodium retention, fluid overload and oedema

Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution should be used with particular caution, in:

- Patients with conditions that may cause sodium retention, fluid overload and oedema (central and peripheral), such as
    - Primary hyperaldosteronism,
    - Secondary hyperaldosteronism associated with, for example,
      - hypertension,
      - congestive heart failure,
      - liver disease (including cirrhosis),
      - renal disease (including renal artery stenosis, nephrosclerosis)
    - Pre-eclampsia.
- Patients taking medications that may increase the risk of sodium and fluid retention, such as corticosteroids.

Hypokalaemia

The infusion of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution may result in hypokalaemia. This medicine should be used with particular caution in patients with or at risk for hypokalemia. Close clinical monitoring may be warranted in, for example:

- persons with metabolic alkalosis
- persons with thyrotoxic periodic paralysis, administration of intravenous dextrose (glucose) has been associated in aggravating hypokalaemia
- persons with increased gastrointestinal losses (e.g., diarrhea, vomiting)
- prolonged low potassium diet
- persons with primary hyperaldosteronism
- patients treated with medications that increase the risk of hypokalaemia (e.g., diuretics, beta-2 agonist, or insulin).

Hypo- and hyperosmolality, serum electrolytes and water imbalance

Depending on the volume and rate of infusion and depending on a patient's underlying clinical condition and capability to metabolize dextrose (glucose), intravenous administration of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution can cause:

- Hypo-osmolality
- Hyperosmolality, osmotic diuresis and dehydration
- Electrolyte disturbances such as
  - hyponatraemia (see above),
  - hypokalaemia (see above),
  - hypophosphataemia,
  - hypomagnesaemia,
- Overhydration/hypervolaemia and, for example, congested states, including central (e.g., pulmonary congestion) and peripheral oedema.

Clinical evaluation and periodic laboratory determinations may be necessary to monitor changes in fluid balance, electrolyte concentrations and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient or the rate of administration warrants such evaluation.

Hyperglycaemia

Rapid administration of dextrose (glucose) solutions may produce substantial hyperglycaemia and a hyperosmolar syndrome. In order to avoid hyperglycaemia the infusion rate should not exceed the patient's ability to utilize dextrose (glucose).

To reduce the risk of hyperglycaemia-associated complications, the infusion rate must be adjusted and/or insulin administered if blood glucose levels exceed levels considered acceptable for the individual patient.

Intravenous dextrose (glucose) should be administered with caution in patients with, for example:

- impaired glucose tolerance (such as in diabetes mellitus, renal impairment, or in the presence of sepsis, trauma or shock),
- severe malnutrition (risk of precipitating a refeeding syndrome, see below),
- thiamine deficiency, e.g., in patients with chronic alcoholism (risk of severe lactic acidosis due to impaired oxidative metabolism of pyruvate),
- water and electrolyte disturbances that could be aggravated by increased dextrose (glucose) and/or free water load.

Other groups of patients in whom Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution should be used with caution include:

- patients with ischemic stroke. Hyperglycaemia has been implicated in increasing cerebral ischemic brain damage and impairing recovery after acute ischemic strokes.
- patients with severe traumatic brain injury (in particular during the first 24 hours following the trauma). Early hyperglycaemia has been associated with poor outcomes in patients with severe traumatic brain injury.
- Newborns (see Paediatric glycaemia-related issues).

Prolonged intravenous administration of dextrose (glucose) and associated hyperglycaemia may result in decreased rates of glucose-stimulated insulin secretion.

Hypersensitivity Reactions

- Hypersensitivity/infusion reactions, including anaphylaxis, have been reported (see section 4.8).

- Stop the infusion immediately if signs or symptoms of hypersensitivity/infusion reactions develop. Appropriate therapeutic counter measures must be instituted as clinically indicated.
- Solutions containing dextrose (glucose) should be used with caution in patients with known allergy to corn or corn products.

Refeeding syndrome

Refeeding severely under nourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intake while avoiding overfeeding can prevent these complications.

Severe renal impairment

Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution should be administered with particular caution to patients at risk of (severe) renal impairment. In such patients, administration may result in sodium retention and/or fluid overload.

Paediatric use

The infusion rate and volume depend on the age, weight, clinical and metabolic conditions of the patient, concomitant therapy, and should be determined by a physician experienced in paediatric intravenous fluid therapy.

Paediatric Population

Intravenous fluid therapy should be closely monitored in the paediatric populations as they may have impaired ability to regulate fluids and electrolytes. Adequate urine flow must be ensured and careful monitoring of fluid balance, plasma and urinary electrolyte concentrations are essential.

Paediatric glycaemia-related issues

Newborns, especially those born premature and with low birth weight, are at increased risk of developing hypo- or hyperglycaemia. Close monitoring during treatment with intravenous dextrose (glucose) solutions is needed to ensure adequate glycaemic control, in order to avoid potential long term adverse effects.

Hypoglycaemia in the newborn can cause, e.g.,
- prolonged seizures,
- coma and
- cerebral injury.

Hyperglycaemia has been associated with
- cerebral injury, including intraventricular haemorrhage,
- late onset bacterial and fungal infection,
- retinopathy of prematurity,
- necrotizing enterocolitis,
- increased oxygen requirements,
- prolonged length of hospital stay and
- death.

Paediatric hyponatraemia-related issues

- Children (including neonates and older children) are at increased risk of developing hyponatraemia as well as for developing hyponatraemic encephalopathy.
- The infusion of hypotonic fluids together with the non-osmotic secretion of ADH may result in hyponatraemia.
- Hyponatraemia can lead to headache, nausea, seizures, lethargy, coma, cerebral edema and death; therefore, acute symptomatic hyponatraemic encephalopathy is considered a medical emergency.
- Plasma electrolyte concentrations should be closely monitored in the paediatric population.
- Rapid correction of hyponatraemia is potentially dangerous (risk of serious neurologic complications). Dosage, rate, and duration of administration should be determined by a physician experienced in paediatric intravenous fluid therapy.

Blood

Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution should not be administered simultaneously with blood through the same administration set because of the possibility of pseudo agglutination or haemolysis.

Geriatric use

When selecting the type of infusion and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No studies have been conducted.

Both the glycaemic and effects on water and electrolyte balance should be taken into account when administering dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution to patients treated with other substances that affect glycaemic control or fluid and/or electrolyte balance.

Drugs leading to an increased vasopressin effect

The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with i.v. fluids (see sections 4.2, 4.4 and 4.8).

- Drugs stimulating vasopressin release, e.g.: chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics.
- Drugs potentiating vasopressin action, e.g.: chlorpropamide, NSAIDs, cyclophosphamide.
- Vasopressin analogues, e.g.: desmopressin, oxytocin, terlipressin.

Other medicinal products increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

Caution is advised in patients treated with

- lithium. Renal sodium and lithium clearance may be increased during administration and can result in decreased lithium levels.
- corticosteroids, which are associated with the retention of sodium and water (with oedema and hypertension).
- diuretics, beta-2 agonist, or insulin, who increase the risk of hypokalemia.
- certain antiepileptic and psychotropic medications that increase the risk of hyponatraemia.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Intrapartum maternal intravenous dextrose (glucose) infusion may result in foetal hyperglycaemia and metabolic acidosis as well as rebound neonatal hypoglycaemia due to foetal insulin production.

Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution should be administrated with special caution for pregnant women during labour particularly if administered in combination with oxytocin due to the risk of hyponatraemia (see section 4.4, 4.5 and 4.8).

Fertility

There is no information on the effects of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution on fertility.

Lactation

dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution can be used during breast-feeding. The potential risks and benefits for each specific patient should be carefully considered before administration.

4.7 Effects on Ability to Drive and Use Machines

There is no information on the effects of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable Effects

The following adverse reactions have been reported in post-marketing experience, listed by MedDRA System Organ Class (SOC), then where feasible, by Preferred Term in order of severity.

Frequencies cannot be estimated from the available data as all listed adverse reactions are based on spontaneous reporting.

System Organ Class	**Adverse reactions (Preferred terms)**	**Frequency**
Metabolism and nutrition disorders	Hypervolaemia	Not known
	Electrolyte imbalance	Not known
	Hospital acquired hyponatraemia*	Not known

	Hyponatraemia*	Not known
Nervous system disorders	Hyponatraemic encephalopathy**	Not known
Cardiac disorders	Cardiac failure	Not known
Renal and urinary disorders	Polyuria	Not known
Immune system disorders	Hypersensitivity	Not known
	Anaphylactic reaction	Not known

*Potential manifestation in patients with allergy to corn, see section 4.4
** Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see sections 4.2 and 4.4).

Adverse reactions may be associated to the medicinal product(s) added to the solution; the nature of the additive will determine the likelihood of any other adverse reactions.

System Organ Class	**Adverse reactions (Preferred terms)**	**Frequency**
Metabolism and nutrition disorders	Hypervolaemia	Not known
Vascular disorders	Vein injury	Not known
	Thrombophlebitis superficial	Not known
General disorders and administration site conditions	Chills	Not known
	Pyrexia	Not known
	Application site infection	Not known
	Application site pain	Not known
	Application site reaction	Not known
	Injection site phlebitis	Not known
	Injection site extravasation	Not known

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

Excess administration of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution can cause:

- Hyperglycaemia, adverse effects on water and electrolyte balance, and corresponding complications. For example, severe hyperglycaemia and severe dilutional hyponatraemia, and their complications, can be fatal.
- Hyponatraemia (which can lead to CNS manifestations, including seizures, coma, cerebral oedema and death).
- Fluid overload (which can lead to central and/or peripheral oedema).
- See also sections 4.4 and 4.8.

When assessing an overdose, any additives in the solution must also be considered.

Clinically significant overdose of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution may, therefore, constitute a medical emergency.

Interventions include discontinuation of administration, dose reduction, administration of insulin and other measures as indicated for the specific clinical constellation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: "Electrolytes with Carbohydrates".

ATC code: B05BB02.

Dextrose 4.3 % w/v and sodium chloride 0.18 % w/v is an hypotonic solution of sodium chloride and dextrose (glucose).

The pharmacodynamic properties of this solution are those of its components (glucose, sodium and chloride).

Ions, such as sodium, circulate through the cell membrane, using various mechanisms of transport, among which is the sodium pump (Na-K-ATPase). Sodium plays an important role in neurotransmission and cardiac electrophysiology, and also in its renal metabolism.

Chloride is mainly an extracellular anion. Intracellular chloride is in high concentration in red blood cells and gastric mucosa. Reabsorption of chloride follows reabsorption of sodium.

Dextrose (glucose) is the principal source of energy in cellular metabolism.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of this solution are those of its components (glucose, sodium, and chloride).

After injection of radiosodium (^{24}Na), the half life is 11 to 13 days for 99% of the injected Na and one year for the remaining 1%. The distribution varies according to tissues: it is fast in muscles, liver, kidney, cartilage and skin; it is slow in erythrocytes and neurones; it is very slow in the bone. Sodium is predominantly excreted by the kidney, but (as described earlier) there is extensive renal reabsorption. Small amounts of sodium are lost in the faeces and sweat.

The two main metabolic pathways of dextrose (glucose) are gluconeogenesis (energy storage) and glycogenolysis (energy release). Dextrose (glucose) metabolism is regulated by insulin.

5.3 Preclinical safety data

The preclinical safety assessment of dextrose 4.3 % w/v and sodium chloride 0.18 % w/v solution for infusion in animals is not relevant as sodium chloride and dextrose (glucose) are physiological constituents of the body and are covered by appropriate pharmacopoeial references.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injection

6.2 Incompatibilities

As with all parenteral solutions, compatibility of the additives with these solutions must be assessed before addition. It is the responsibility of the physician to judge the incompatibility of an additive medication with the corresponding sodium chloride and dextrose solution, by checking for eventual colour change and/or eventual precipitate, insoluble complexes or crystals apparition. The instructions for use of the medication to be added must be consulted. Before adding a drug, verify it is soluble and stable in water at the pH of the corresponding sodium chloride and dextrose solution.

When a compatible medication is added to the sodium chloride and dextrose solution, the solution must be administered immediately.

Those additives known to be incompatible should not be used.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The product should be used immediately after opening.

In-use shelf-life (Additives)
From a microbiological point of view, the diluted product must be used immediately unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Store below 25ºC.

6.5 Nature and contents of container

Dextrose 4.3 % and 0.18 % sodium chloride Vioser solution for infusion is available in low density polyethylene bottles (round and oval) of 500 ml and 1000 ml.
Each pack contains 10 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use only if the solution is clear, without visible particles and if the container is undamaged.

Do not use the solution after its expiry date.

Each plastic bottle has a protective cap. The protective ring is removed just before use with a simple pull and the infusion device is adjusted in the special elastic slot. Administer immediately following the insertion of infusion set.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique.

The equipment should be primed with the solution in order to prevent air entering the system.

Additives may be introduced before infusion or during infusion through the injection site.

When additive is used, verify isotonicity prior to parenteral administration. Thorough and careful aseptic mixing of any additive is mandatory. Solutions containing additives should be used immediately and not stored.

Adding other medications or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In case of an adverse reaction, infusion must be stopped immediately.

Discard after single use.

Discard any unused portion. No special requirements for disposal.

Do not reconnect partially used containers.

Do not administer the content if:
a) it is not clear and the bottle is not intact,
b) disinfection with 70% alcohol has not taken place:
-on the surface below the site of insertion of the infusion set.
-any other perforation site.

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,
Ha-shiloah 6, POB 7641, Petach Tiqva 4917001, Israel.

9 MARKETING AUTHORISATION NUMBER
171-03-36200-00

Revised in May 2023 according to MOHs guidelines.