SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sodium Chloride Grifols 0.9% w/v Solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL of solution contain:

Sodium chloride 0.9 g

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear and colourless aqueous solution.

The calculated osmolarity of the solution is 308 mOsm/L and pH is 4.5-7.0. The theoretical sodium and chloride content is 154 mmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of dehydration with salt loss
- Treatment of hypochloremic metabolic alkalosis
- In the management of hypovolemia
- Vehicle for the administration of compatible drugs and electrolytes.

4.2 Posology and method of administration

Posology

Treatment of dehydration with salt loss, treatment of hypochloremic metabolic alkalosis and in management of hypovolemia:

Dosage can be varied as directed by a physician. The volume and the average infusion rate must always be adjusted to the patient clinical requirements depending upon the age, weight, clinical condition (e.g. burns, surgery, head-injury, infections), electrolytes and fluid balance, and acid-base balance. In general, it is recommended to administer the solution at an average infusion rate of 40 to 60 drops per minute (120-180 mL/h).

Fluid balance, serum electrolytes and acid-base balance may need to be monitored before and during administration, with particular attention to serum sodium 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 hospital acquired hyponatraemia (see sections 4.4, 4.5 and 4.8).

Concomitant therapy should be determined by the consulting physician experienced in paediatric intravenous fluid therapy (see sections 4.4. and 4.8).

When administering this solution, the total daily fluid requirement must be considered.

The daily recommended dose of fluid is the following:
- adults: 25-35 mL/kg
- children: < 10 kg body weight: 100 mL/kg
  10-20 kg body weight: 1000 mL + 50 mL/kg for every kg over 10 kg
  > 20 kg body weight: 1500 mL + 20 mL/kg for every kg over 20 kg

In adults, the maximum daily dose of fluid is 40 mL/kg (corresponding to 6 mmol of sodium/kg) not exceeding 3000 mL, and the maximum infusion rate is 5 mL/kg/h. Children rarely need more than 2500 mL for males and 2000 mL for females.

In case of acute plasma volume depletion (e.g. imminent or evident hypovolemic shock) the amount of solution should be 3 or 4 times the lost blood volume.

Vehicle for the administration of compatible drugs and electrolytes:

When Sodium Chloride Grifols 0.9% w/v is used as a vehicle for the administration of compatible drugs and electrolytes, the administered dosage and the speed of the infusion will depend on the nature and the dose of the prescribed medicinal product.

Method of administration

Sodium Chloride Grifols 0.9% w/v is intended for intravenous administration by means of infusion.

Precautions to be taken before handling or administering the medicinal product:

Before administration, it must be checked that:
- There is no leakage (by squeezing the bag firmly).
- The solution is clear and without particles.

Do not administer otherwise.

For other instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Sodium Chloride Grifols 0.9% w/v is contraindicated in patients with:

- Hyperhydration states
- Hyperchloremia
- Hypernatremia
- Acidosis

4.4 Special warnings and precautions for use

Sodium Chloride Grifols 0.9% w/v is an isotonic solution.

- The solution should be administered with caution in case of hypertension including pre-eclampsia/eclampsia, congestive heart failure, pulmonary or peripheral edema, severe renal insufficiency, decompensated cirrhosis, primary hyperaldosteronism, as well as in patients receiving corticosteroids or ACTH (see section 4.5).

- The product should be administered with caution to patients with hypokalaemia because this condition may worsen the pre-existing electrolyte imbalance and cause cardiovascular complications, especially in patients with heart disease.

  It also should be administered with great care to elderly patients because they are more likely to have impaired renal and cardiac function.

- High volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure, and in patients with non-osmotic vasopressin release (including SIADH), due to the risk of hospital acquired hyponatraemia (see below).

  Hyponatraemia:

  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 and even isotonic fluids.

  Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (cerebral oedema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with cerebral 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.

- Periodic laboratory determinations are necessary to monitor changes in fluid balance, serum electrolyte concentrations, and acid base balance during prolonged therapies or

whenever the condition of the patient require such evaluation, as in the case of patients with imminent or existing acid-base imbalance.

- Sodium re-equilibration should not be performed at a too rapid rhythm, especially due to the risk of occurrence of serious neurological complications such as osmotic demyelination syndrome (see sections 4.2 and 4.9).

- Sodium chloride 0.9% solution should be administered only for short period therapy as a prolonged administration could lead to a metabolic acidosis.

- Because of the administration technique, extravasation and/or thrombophlebitis may occur during intravenous infusion (see section 4.8). Extravasation may lead to tissue damage (local pain, erythema, burning, pruritus, swelling and ulceration) at the site of injection or along the vein. Thrombophlebitis may occur if the solution is continuously administered in the same site of injection. In these cases, intravenous infusion should be stopped and appropriate therapeutic measures should be instituted. Possible signs of inflammation at the injection site must be checked periodically.

- Due to the risk of air embolism, particular care must be taken in the handling of the administration sets (see section 6.6).

When adding a medicinal product to the solution, compatibility, clarity and colour before use must be checked (see section 6.2). Do not store the mixture (see section 6.6).

Paediatric population

Term and preterm neonates may retain sodium in excess due to an immature renal function. Therefore, in these cases, repeated sodium chloride infusions should only be performed after determining serum sodium levels.

There are no other specific warnings or precautions to paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Sodium chloride interacts with lithium carbonate, whose renal excretion is directly proportional to the sodium levels in the body. Thus, sodium chloride infusion accelerates renal lithium excretion, leading to a decrease in its therapeutic action.

Intravenous sodium chloride solutions should be administered with caution to patients receiving corticosteroids or ACTH, since they favour water and sodium retention.

Drugs leading to an increased vasopressin effect:

The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with intravenous 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, vasopressin, terlipressin)

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data recorded in scientific literature on a large number of exposed pregnancies indicate that maternal infusion of sodium chloride solutions during pregnancy does not cause any harmful effects on the fetus or neonate.

Sodium Chloride Grifols 0.9% should be administrated with special caution for pregnant women during labour particularly as to serum sodium if administered in combination with oxytocin (see sections 4.4, 4.5 and 4.8).

Caution is advised in patients with pre-eclampsia (see section 4.4).

Breast-feeding

Sodium chloride is excreted in human milk. Both electrolytes, sodium and chloride, are natural constituents of human milk and therefore no side effects on the breastfed infant are expected following maternal intravenous administration of therapeutic doses.

Fertility

There are no data regarding fertility and use of sodium chloride solutions but no side effects are anticipated.

When an additive is used, the nature of the additive and its use during pregnancy and lactation should be evaluated separately.

The physician should carefully consider the potential risks and benefits for each specific patient before administering Sodium Chloride Grifols 0.9% w/v.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Pain or local reaction, fever, infection, extravasation, venous thrombosis and phlebitis extending from the site of injection may occur if it is continuously administered in the same infusion site.

Hyperhydration, hypernatremia, hyperchloremia, hypervolemia and related signs, such as formation of edemas or metabolic acidosis due to the decrease of bicarbonate concentration, may occur following an inadequate or excessive administration of normal saline solution.

Patients with non-osmotic vasopressin release, patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists are at particular risk of acute hyponatraemia

upon infusion of hypotonic and even isotonic fluids. Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see sections 4.2, 4.4 and 4.5).

The frequency of these adverse reactions cannot be estimated from the available data.

List of adverse reactions:

System Organ Class	*Adverse reactions*	*Frequency*
Metabolism and nutrition disorders	Metabolic acidosis Hyperchloremia Hypernatremia Hyperhydration Hypervolemia Hospital acquired hyponatraemia	Not known
Nervous system disorders	Acute hyponatraemic encephalopathy	Not known
Vascular disorders	Venous thrombosis Phlebitis	Not known
General disorders and administration site conditions	Edema Pyrexia Infection Injection site local pain or reaction Extravasation	Not known

If the solution is used as a vehicle for the administration of other compatible drugs, other adverse reactions attributable to the nature of these added drugs may also occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: https://yellowcard.mhra.gov.uk or telephone 0808 100 3352.

4.9 Overdose

Excessive intravenous administration of sodium chloride may lead to fluid overload (hypervolemia, hyperhydration) and/or solute overload (hypernatremia and hyperchloremia). If it occurs, administration should be discontinued and appropriate therapeutic countermeasures should be instituted.

Fluid overload may result in pulmonary and/or peripheral edema and their consequent effects (heart failure).

An excessive intravenous administration of sodium may lead to development of hypernatremia leading to intracellular dehydration, which should be treated in specialised area. The general symptoms related to hypernatremia can include nausea, vomiting, diarrhea, abdominal cramps, thirst, reduced salivation and lacrimation, fever, sweating, tachycardia, hypertension, headache, dizziness, restlessness, irritability, weakness, lipothymia, muscular twitching and rigidity, somnolence,

confusion progressing to convulsions, coma, renal failure, cerebral, peripheral and pulmonary edema, respiratory arrest, and death.

Serious neurological complications such as osmotic demyelination syndrome can occur several days after too important and/or too rapid correction of hyponatremia (see sections 4.2 and 4.4). Clinical signs of osmotic demyelination syndrome are progressive: confusion, dysarthria, dysphagia, weakness of the limbs, tetraplegia, delirium and finally coma.

Excessive administration of chloride may cause hyperchloremia and hence, there is a loss of bicarbonate with an acidifying effect. Often hyperchloremia does not produce any symptoms. In cases where symptoms develop, they are similar to those of hypernatremia.

When Sodium Chloride Grifols 0.9 % w/v is used as vehicle for the administration of compatible drugs and electrolytes, other signs and symptoms of excessive infusion may arise from the added medicinal product. In the event of accidental excessive infusion, treatment should be stopped and patients monitored for any clinical signs and symptoms associated with the medication given. Symptomatic treatment and appropriate support should be given in accordance with requirements.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intravenous solutions affecting the electrolyte balance – Electrolytes, ATC code: B05BB01.

Sodium chloride, the active substance of Sodium Chloride Grifols 0.9% w/v, is the main salt involved in the tonicity of extracellular fluid. Sodium, essential and irreplaceable, is the main cation of extracellular fluid and the main osmotic component in the control of blood volume. However, chloride ion may be replaced by bicarbonate ion, always available in the form of carbon dioxide through the cell metabolism. The 0.9% sodium chloride solution shows the same osmotic pressure as body fluids.

The administration of isotonic sodium chloride solution is particularly indicated in cases of dehydration accompanied by salt loss as well as in the management of hypovolemia.

On the other hand, disorders of water and electrolytes metabolism are often accompanied by disturbances in the acid-base balance. In cases of hypochloremic metabolic alkalosis, administration of normal saline will restore the lost chloride ion, whereas the excess of bicarbonate will be excreted through the kidneys, with the subsequent fall and normalization of the alkaline reserve.

Likewise, isotonic sodium chloride solution is a suitable vehicle for the intravenous administration of many compatible drugs and electrolytes.

5.2 Pharmacokinetic properties

Due to its intravenous administration, absorption does not take place.

Sodium and chloride electrolytes will be mainly distributed throughout the extracellular fluid. Since normal saline solution is isotonic, its administration will not cause changes in the osmotic pressure of the extracellular fluid, therefore water will not pass towards the intracellular compartment and both ions will almost not enter the cell.

However, a decrease (by diluting) in the oncotic pressure of plasma proteins will take place, with water passing towards the interstitial compartment through the capillary walls, thereby achieving normality.

It must be taken into account that the richest tissue in water is muscle tissue whereas sodium is mainly found in bone tissue, being both their main reserves.

Sodium will be excreted mainly by the kidneys (95%) and the rest through the skin (perspiration) and digestive tract.

On the other hand, water will be eliminated through the kidneys, skin, lungs and digestive tract.

Therefore, kidneys are the most important organ for the maintenance of the extracellular sodium concentration, excreting more or less quantity of this cation according to the body requirements, and being even capable of producing urine with concentrations lower than 1 mEq sodium/l.

5.3 Preclinical safety data

No safety preclinical studies have been conducted with this medicinal product. All components are naturally present in the body and their biochemical properties are well known. Therefore, toxic effects are not to be expected if instructions are followed correctly.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

The compatibility of additives with Sodium Chloride Grifols 0.9% w/v should be checked before adding a medicinal product.

It is the responsibility of the physician to determine the incompatibility of an additive medicinal product with respect to the Sodium Chloride Grifols 0.9% w/v and the container by monitoring any discoloration and/or formation of precipitates, insoluble complexes or crystals. The Instructions for Use of the medication to be added must be consulted.

Before adding a medicinal product, verify it is soluble and stable in water at the pH of Sodium Chloride Grifols 0.9% w/v.

When a compatible medication is added to Sodium Chloride Grifols 0.9% w/v, the solution must be administered immediately.

Sodium Chloride Grifols 0.9% w/v is physically incompatible with amphotericin B, an antifungal chemotherapic agent.

This medicinal product must not be mixed with other medicinal products unless their compatibility is verified.

6.3 Shelf life

- 18 months (for the 50 mL format)
- 2 years (for the 100 mL, 250 mL, 500 mL and 1000 mL formats).

Once the container is opened, the solution must be used immediately (see section 6.6).

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Sodium Chloride Grifols 0.9% is packaged in polypropylene flexible bags (Fleboflex) containing 50 mL, 100 mL, 250 mL, 500 mL and 1000 mL of solution in the following presentations:

- 50 mL x 115 bags
- 100 mL x 70 bags
- 250 mL x 28 bags
- 500 mL x 20 bags
- 1000 mL x 10 bags

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Discard after single use.

Discard any unused portion.

Do not store solutions containing additives.

Do not reconnect partially used bags.

Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

When introducing additives to sodium chloride 0.9% solution as well as when administering the solution, aseptic technique must be used.

Mix the solution thoroughly when additives have been introduced.

To connect the infusion set, separate the protecting tab from the infusion port so that the membrane of access to the bag is exposed. Remove all air from the syringe and associated tubing prior to infusion to avoid air embolism.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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