SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION 50-100-150-250-500-1000 and 3000 ml PVC Bag

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each 100 ml solution contains 0.9 g of sodium chloride.

Excipients:

For excipients, see section 6.1.

The Osmolarity of the solution is 308 mOsmol/l.

Ion concentrations of the solution are:

- sodium: 154 mEq/l
- chloride: 154 mEq/l

3. PHARMACEUTICAL FORM

Sterile and solution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION is indicated for:

- Treatment of isotonic extracellular dehydration
- Treatment of sodium losses
- As a diluent for compatible drugs in parenteral administrations

4.2 Posology and method of administration

Posology /frequency and duration of administration

Each dose should be adjusted by the physician; according to the age, weight, clinical condition and hydration status of the patient. Serum electrolyte concentrations should be monitored closely during administration.

Unless recommended otherwise by the physician, it should be used as 500-3000 ml/kg for 24 hours in adolescents and elderly, 20-100 ml/kg for 24 hours in infants and children for the treatment of extracellular dehydration and sodium loss.

When used as a diluent for other drugs, the dose should be adjusted according to the nature of the drug and the dosage scheme. Generally, 50-250 ml of fluid is sufficient.

The frequency of administration and the dose is adjusted by the physician according to patient's clinical condition.

When used as a drug diluent, the recommended infusion rate for Biofleks 0.9% isotonic sodium chloride solution is adjusted according to the dose of the drug to be diluted.

Method of administration:

It is administered intravenously with sterile non-pyrogenic sets through peripheral or central veins.

For the details on administration, also see Section 6.6.

Additional information on special populations:

Renal/Hepatic impairment:

Since there are no studies conducted for this population, no special dose recommendation is available for this patient group.

Pediatric population:

The administration dose and infusion rate are adjusted by physician according to patient's weight, clinical and biological status, and intended treatment, similarly as in adults.
It is generally recommended as 20-100 ml/kg for 24 hours for this population.

Geriatric population:

The administration dose and infusion rate are adjusted by physician according to patient's weight, clinical and biological status, and intended treatment, similarly as in adults.

4.3 Contraindications

The solution is contraindicated in patients with hypernatremia or hyperchloremia.

Also it should not be used in cases where sodium or chloride administration is clinically harmful.

4.4 Special warnings and precautions for use

Administration of solutions may lead to fluid and/or solute load, which causes dilution in serum electrolyte concentration, overhydration, congestive conditions, or pulmonary edema. The risk of dilution is inversely correlated with electrolyte concentration. The risk of developing congestive conditions which may cause peripheral and pulmonary edema is directly correlated with the electrolyte concentration in the solution.

The solution contains 154 mmol/l sodium (Na^+) and 154 mmol/l chloride (Cl^-); its osmolarity is approximately 308 mOsm/l, and pH is 5.5 (4.5 - 7.0).

All intravenous infusions initially require careful clinical monitoring.

Administration should be performed under regular and careful supervision. Clinical and biological parameters, especially serum electrolyte levels should be monitored.

Sodium retention may occur in premature and newborn babies due to underdeveloped renal functions. Thus, repeating sodium chloride infusions in newborns should be applied after the

determination of serum sodium levels.

Solutions containing sodium should be used with caution in conditions such as hypertension, cardiac insufficiency, peripheral or pulmonary edema or impaired renal function, preeclampsia, aldosteronism or other conditions and treatments (eg. corticosteroid treatment) that cause sodium accumulation.

Pseudohyponatremia is a condition where conventional calculation method for plasma sodium gives false results even though it's not the case. It develops when large molecule concentration levels are abnormally high and plasma water level is abnormally low. It has been reported that it can also be seen in patients with diabetes mellitus, in addition to hyperlipemia and hyperproteinemia. Actual values can be obtained by evaluating the concentration to the plasma water level.

Excessive application of potassium-free solutions can lead to significant hypokalaemia cases. Serum potassium levels should be maintained at normal and potassium should be added to the treatment if necessary.

To reduce any risk of incompatibility with drugs added to the solution to minimum, the final mixed solution should be observed for blurriness and precipitation right after mixing, before and during administration at regular intervals.

If the administration is going to be done with a controlled infusion pump, it should be made sure that the pump has stopped before the bag is completely empty to avoid air embolism.

The solution should be infused intravenously via sterile sets. It is advised that intravenous sets are changed every 24 hours.

It should only be used if the bag is intact and not leaking.

Laboratory tests: When the prolonged parenteral treatment or patient's condition requires, clinical assessment and periodical laboratory tests should be performed to monitor the changes in fluid balance, electrolyte concentration, and acid-base balance. When significant deviations from normal values are observed, these values should be normalized with alternative solutions.

Precautions and warnings for paediatric use: Liquid and electrolyte balance in newborns and infants may be affected by administration of liquids in very small amounts. Newborns, especially prematures with underdeveloped renal functions and has limited capability to excrete solutes with liquid should be treated carefully. Liquid intake, urine amount and serum electrolyte levels should be closely monitored.

Precautions and warnings for use in elderly: Generally, dose must be selected carefully in elderly patients. The treatment should generally be started with the lowest doses from the dosage range since the risk of having impaired renal, hepatic or cardiac functions is higher and also concurrent illnesses and drug use is more common in elderly patients.

4.5 Interaction with other medicinal products and other forms of interaction

Some of the drugs and other solutions added may be incompatible with the solution. Like all parenteral solutions, compatibility with additive drugs should be assessed by the physician before use.

If other substances are to be added to the solution, aseptic technique should be used and shaken until mixed. Color change, insoluble particles and crystallization should not be observed after adding drugs into BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION.

Regarding its sodium content, caution should be excersized when the solution is administered with corticosteroids and carbenoxolon as it may cause a risk for sodium and water retention.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women of childbearing potential/Birth Control (Contraception)

Since there are no data on the effects of BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION in women of childbearing potential and birth control, there are no recommendations about the use of a contraception method after BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION administration.

Pregnancy

There are no adequate data from the use of isotonic sodium chloride solutions in pregnant or lactating women.

Animal researches are not sufficient for effects on pregnancy and/or embryonal/fetal development and/or labor and/or postnatal development (see Section 5.3). The potential risk for humans is unknown.

BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION should not be used during pregnancy unless it is considered to be clearly essential.

No animal breeding studies have been performed with sodium chloride containing solutions. It is not known weather BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION might cause damage on the fetus when administered in pregnant women or impair reproduction.

BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION should only be used by pregnant women if clearly necessary.

Labor

When BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION is used during labor and delivery, effects on subsequent growth, development, and functional maturation of the baby due to effects of the duration of labor, effects of labor by forceps or other interventions, or other interventions that need to be performed in the newborn are not known.

In literature, solutions containing dextrose and sodium chloride have been reported to be used during labor and delivery. The fluid balance, glucose and electrolyte concentration, and acid-base balance of the mother and fetus should be assessed regularly and when required by the status of the fetus.

Lactation period

It is not known whether this drug is excreted in breast milk. Since it is known that many drugs are excreted in breast milk, BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION must be used with caution in lactating women.

4.7 Effects on ability to drive and use machines

Driving during the use of solutions administered via infusion is not practically possible. After administration, it does not have any known effects on ability to drive and use machines.

4.8 Undesirable effects

Under normal treatment conditions, undesirable effects are not likely to occur.

Undesirable effects might originate from the deficiency or excessivene ss of ions in the solution; thus sodium and chloride levels should be closely monitored. Caution should be used regarding the possibility that the additional medications diluted in and administered also cause adverse effects. In such cases, see product information of the additional medication administered.

Inattentive administration of intravenous sodium chloride treatment (eg. in the postoperative period, in patients with cardiac or renal impairment) can lead to hypernatremia. Osmotically induced water movement can lead to thrombosis and haemorrhage by dehydration of internal organs, especially the brain, by reducing intracellular volume.

When any addition is made to the isotonic solutions to make the solution hypertonic, if the application is done subcutaneously, there may be pain at the injection site.

When administered in large volumes, sodium retention, edema and hyperchloremic acidosis may occur. If adverse effects are observed during administration, infusion should be stopped, patient should be assessed, appropriate therapeutic measures should be taken,

Very common (≥1/10); common (≥1/100 - <1/10); uncommon (≥1/1000 - <1/100); rare (≥1/10000 - <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

The adverse effects indicated below, may occur due to overdosing or excess sodium or chloride or administration technique. Their frequency is unknown (can affect so few patients that cannot be estimated from the available data).

Blood and lymphatic system disorders

Unknown: Thrombosis; Haemorragia

Metabolism and nutritional disorders

Unknown: Sodium retention; Water retention and edema; exacerbation of congestive heart failure (due to hypernatremia); Hyperchloremic acidosis.

Nervous system disorders

Unknown: Headache, dizziness, restlessness, irritation, convulsions, coma and death (dehydration due to hypernatremia).

Cardiac disorders

Unknown: Tachycardia (due to hypernatremia).

Vascular disorders

Unknown: Hypertension (due to hypernatremia).

Respiratory, thoracic and mediastinal disorders

Unknown: Pulmonary edema, respiratory depression and respiratory arrest (due to hypernatremia).

Gastrointestinal disorders

Unknown: Nausea, vomiting, diarrhea, abdominal cramps, thirst, decreased amount of saliva (due to hypernatremia).

Skin and subcutaneous tissue disorders

Unknown: Decreased perspiration (due to hypernatremia).

Musco-skeletal disorders, connective tissue and bone disorders

Unknown: Muscle stiffness and twitches (due to hypernatremia).

Renal and urinary disorders

Unknown: Renal insufficiency (due to hypernatremia).

General disorders and administration site conditions

Unknown: Fever; Fatigue (due to hypernatremia); Pain at the injection site (due to subcutaneous administration of solution which was made hypertonic with additives).

Surgical and medical procedures

Unknown: Febrile reactions; Infection on the injection site; Venous thrombosis or phlebitis extending from the injection site; Extravasation and hypervolemia (adverse effects due to administration technique)

Reporting of adverse effects

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose and treatment

Adverse reactions occur due to excess of sodium include nausea, vomiting, diarrhea, abdominal cramps, thirst, decrease amount of saliva, tears and sweat, fever, tachycardia, hypertension, renal insufficiency, peripheral and pulmonary edema, respiratory arrest, headache, dizziness, restlessness, irritation, fatigue, muscle stiffness and twitches, convulsions, coma and death.

Excessive chloride accumulation in the body can cause loss of bicarbonate and acidic shift in body fluids.

If fluid or solute loading due to excessive infusion occurs during parenteral therapy, the patient should be reassessed and appropriate corrective treatment should be initiated.

Diuretics may be used in the treatment of the edema due to isotonic expantion ointment and appropriate replacement treatment should be used to avoid fluid-electrolyte imbalance. Treatment for hypervolemic hypernatremia requires withdrawal of sodium more than water, and can be done by compensation of diuretic-induced sodium and water loss with only water. Main reason of the treatment is to normalize the volume and composition of body fluids.

If the overdose is related to the medications added to the solution, signs and symptoms caused by overdose are dependent on the properties of the medication added. In case of accidental overdose during treatment, the administration should be stopped and the patient should be observed for the symptoms and signs related to the medication. If necessary, symptomatic and supportive treatments should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intravenous solutions / Solutions affecting electrolyte balance

ATC code: B05XA03

When used for the maintenance of fluid and electrolyte balance, the pharmacodynamic properties of the fluid is made up of the properties of sodium and chloride it contains.

Ions like sodium pass through the cell membrane using various transport mechanisms such as sodium pump (Na-K-ATPase). Sodium has an important function on neurotransmission, cardiac electrophysiology and renal metabolism.

Chloride is an anion essentially found in extracellular fluid. Intracellular chloride is found in high concentrations in red blood cells and gastric mucosa. The reuptake of chloride follows the reuptake of sodium.
The pharmacodynamic properties of the added medicinal drugs, pharmacodynamics of the added drug.

5.2 Pharmacokinetic properties

General properties

The pharmacokinetic properties of BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION is made up of the properties of its compounds (sodium and chloride).

Absorption:
The active substances in intravenously-administered drugs reach their maximum plasma concentrations immediately after the administration.

Distribution:
Sodium distribution varies according to the tissues, it is fast in muscles, liver, kidneys, cartilages and skin, slow in neurons, and very slow in bones.

Chloride is mainly distributed in extra-cellular fluids.

Biotransformation:

The half-life after injection with radiolabeled sodium (^{24}Na) is 11-13 days for 99% of the sodium and one year for the remaining 1%.

Chloride is closely related to sodium metabolism and reflects the acid-base balance of the body via its concentrations.

Elimination:

Sodium is excreted and mostly reabsorbed mainly by renal route. A low amount of sodium is

excreted via feces and sweat.

As chloride is metabolically related to sodium it is mainly excreted via the kidneys and small amounts are excreted via feces and sweat.

Linearity/non-linearity:

The electrolytes contained in 0.9% isotonic sodium chloride solution when administered at a rate which can make up the deficiencies in the body, i.e. at therapeutic dose, exhibit a linear pharmacokinetics.

5.3 Pre-clinical safety data

Since the components of the solution are physiological components of animal and human plasma, no toxic effects are expected in clinical practice and thus no studies have been conducted on carcinogenicity, mutagenic potential and fertility with 0.9% isotonic sodium chloride solution.

The safety of the medications that are added to the solution should be separately considered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

Compatibility of the medication which will be added to the solution should be assessed in advance. In the absence of the compatibility data, the solution should not be mixed with another medication.

The physician who performs the administration is responsible for deciding whether the medication added is compatible by checking the presence of color changes and/or precipitation, undissolved compounds or crystallization following the addition of the medication. To decide whether the medication intended to be added to BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION is compatible or not, the leaflet of the additional medication should be referred.

Before adding a medication to the solution, its solubility and stability in the pH of BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION should be confirmed.

After addition of a compatible medication, BIOFLEKS 0.9% ISOTONIC SODIUM CHLORIDE SOLUTION should be immediately used.

Drugs known to be incompatible should not be added.

6.3 Shelf life

24 months

In-use shelf life when used as a diluent: From a microbiological perspective, it should be used right after it is prepared for application. If not used immediately, the determination of storage conditions and duration is the responsibility of the person who mixed/diluted the solution; when it is not performed under validated aseptic conditions it is normally no longer than 24 hours between 2-8°C.

6.4 Special precautions for storage

24 It should be stored at room temperature below 25°C.

6.5 Nature and contents of container

50, 100, 150, 250, 500, 1000, 3000 ml PVC Bag with two outputs, with protective HDPE Overpouch. The product is available with or withouta set.

6.6 Special precautions for disposal and other handling

Instructions for Use

The solution should be checked before use.

Administer intravenously with sterile non-pyrogenic sets.

Only clear, particle-free products with intact package integrity should be used. Administration should be started immediately after the administration set is attached to the product.

In order to avoid air embolism due to possible residual air contained in the bag, do not connect in series to other infusion fluids.

Pressurizing intravenous solutions contained in flexible plastic bags to increase flow rates can result in air embolism if the residual air in the bag is not fully evacuated prior to administration.

The solution should be administered with aseptic technique via a sterile administration set. In order to prevent air entry into the system, fluid should be passed through the administration set before use.

Additional medications may be added before or during infusion through the injection port with a needle in aseptic conditions. The isotonicity of the final product should be determined before parenteral administration.

The added medication should be completely mixed with the solution before administration to the patient. The solutions containing additional medication should be used immediately after the addition of the medication; it should not be kept for later use.

Adding an additional medication to the solution or incorrect administration technique may result in fever reaction due to pyrogenic contamination of the product. In case of any adverse reaction, infusion should be stopped at once.

For single use.

Partially used solutions should not be stored; they should be destroyed in line with medical waste procedures at the healthcare center where intravenous administration was performed. Partially-used bags should not be reconnected to the systems administered to patient.

To open it:

1. Check the integrity of outer packaging and whether there is any leakage; if the packaging is damaged do not use it.
2. Tear and open the protective outer packaging.
3. Check if the bag inside the protective packaging is intact by squeezing. Check the clarity of the solution and if there are any foreign substances inside the solution.

Preparation for administration:

1. Hang the bag.
2. Remove the protective cap on the administration port.
3. Firmly insert the spike of the administration set to the administration port.
4. Follow the instructions for use of the set to administer the solution to the patient.

Adding additional medication:

Caution: As with all parenteral solutions, all substances that will be added to the product should be compatible. If a medication is to be added to the product, the compatibility of the final mixture should be checked before administration to the patient.

Adding a drug before administration

1. Disinfect the medication administration port.
2. Administer the medication through the medication administration port via a syringe with a 19-22 gauge needle.
3. Mix the solution and the medication well. For dense medications such as potassium chloride, gently tap the administration port when it's on upright position to ensure that it is mixed.

Caution: The bags which were mixed with other medications should not be stored.

Adding medication during administration

1. Close the clamp of the set.
2. Disinfect the medication administration port.
3. Administer the medication through the medication administration port via a syringe with a 19-22 gauge needle.
4. Take the solution from the hanger and bring it to an inverted position.

5. At this position, gently tap the administration port and injection port to ensure that the solution and the additional medication are mixed.
6. Invert the bag to its original position, open the clamp and continue the administration.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

195/81

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 23.10.2000

Date of renewal of the authorization: 30.01.2006

10. DATE OF REVISION OF THE SmPC

03/02/2015