SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PF 0.9% Isotonic Sodium Chloride Solution for I.V. Infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each 100 ml of solution contains 0.9 g sodium chloride.

Excipients:
For a full list of excipients, see section 6.1.
Osmolarity of solution is 308 mOsmol/l.

Ionic concentrations of solution:
- Sodium: 154 mEq/l
- Chloride: 154 mEq/l

3. PHARMACEUTICAL FORM

Sterile solution for intravenous infusion.
Clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PF 0.9% ISOTONIC SODIUM CHLORIDE is indicated for:
- Treatment of isotonic extracellular dehydration
- Treatment of sodium depletion
- As diluent of compatible drugs for parenteral administration.

4.2 Posology and method of administration

Posology/frequency and duration of administration

The dosage is to be individualised by the physician depending on age, weight, clinical condition and in particular the patients's hydration state Serum electrolyte concentrations must be monitored during treatment.

In general, 500 to 3000 ml per 24 hours for adults, adolescents and elderly and 20 to 100 ml/kg per 24 hours for infants and children is recommended for treatment of isotonic extracellular dehydration and sodium depletion unless otherwise prescribed by the doctor.

The dosage when used as a diluent should be determined by the nature and the dose regimen of the diluted drug. In general 50 to 250 ml of fluid is sufficient.

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

When PF 0.9% ISOTONIC SODIUM CHLORIDE is used as a diluent, the infusion rate will be adjusted according to the nature and the dose regimen of the diluted drug.

Method of administration:
The administration is to be made by intravenous route in a peripheral or central vein using sterile, apyrogenic sets.

See also section 6.6 for details on the administration.

Additional information on special populations:

Renal/Hepatic failure:
No dosage recommendations are made for this patient group, as there is no specific study for this population.

Pediatric population:
As in adults, dosage and infusion rate are directed by a physician depending on weight, clinical and biological condition of the patient and the concomitant treatment.

In general 20 to 100 ml per 24 h and per kg is recommended in this population.

Geriatric population:
As in adults, dosage and infusion rate are directed by a physician depending on weight, clinical and biological condition of the patient and the concomitant treatment.

4.3 Contraindications
The solution is contra-indicated in patient presenting hypernatraemia or hyperchloraemia.

It is also contraindicated where the administration of sodium or chloride could be clinically detrimental.

4.4 Special warnings and precautions for use
The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilution is inversely proportional to the electrolyte concentration. The risk of

congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration.

The solution contains 154 mmol/l sodium (Na^+) and 154 mmol/l chloride (Cl^-); the osmolarity is about 308 mOsm/l and the pH is 5.5 (4.5-7).

Careful clinical monitoring is required at the beginning of any intravenous infusion Administrations should be periodically and carefully monitored. Clinical and biological parameters, in particular serum electrolyte concentrations should be monitored.

In preterm or term neonates, sodium retention can be seen because renal function is not yet fully developed. Repeated infusions of sodium chloride in neonates should therefore only be given after determination of the serum sodium levels.

Sodium-containing solutions should be used with caution in cases of hypertension, heart failure, peripheral or pulmonary edema, impaired renal function, preeclampsia, aldosteronism or other conditions and treatments with sodium accumulation (e.g. corticosteroid therapy).

Pseudohypononatraemia is a condition in which plasma sodium is false low as measured by conventional methods in spite of the fact that it is not actually low. This may occur when large molecules are at a high concentration at an abnormally high level and, consequently, when the plasma water ratio falls abnormally. It has been reported that associated hyperlipemia and hyperproteinemia can also be seen in patients with diabetes mellitus. Real values can be obtained by evaluating the concentration based on plasma/water ratio.

Excessive administration of potassium-free solutions may result in significant hypokalemia. Serum potassium levels should be maintained and potassium supplemented as required.

To minimize the risk of possible incompatibilities arising from mixing any of these solutions with other additives that may be prescribed, the final mixture should be inspected for cloudiness or precipitation immediately after mixing, prior to administration and periodically during administration.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the bottle runs dry or air embolism may result.

Solution is intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

Use only if solution is clear and container and seals are intact.

<u>Laboratory tests:</u>
Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral

therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require normalization of these values with alternative solutions.

Warnings and precautions for pediatric use:

In neonates or in very small infants even small volumes of fluid may affect fluid and electrolyte balance.

Care must be exercised in treatment of neonates, especially pre-term neonates, whose renal function may be immature and whose ability to excrete fluid and solute loads may be limited. Fluid intake, urine output, and serum electrolytes should be monitored closely.

Warnings and precautions for use in elderly:
In general, dose selection for an elderly patient should be cautious. Starting at the low end of the dosing range is recommended in elderly considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This medicinal product contains 154 mmol sodium per liter. This should be considered for the patients subjected to controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Some of the drugs and solutions added to the solution may be incompatible. As in all parenteral solutions, compatibility with additional medication should be evaluated by the physician.

If other substances are to be added to the solution, aseptic technique should be used and shaken until mixed. It should be ensured that there is no discoloration, insoluble particles and crystallization after the drugs are added into PF 0.9% ISOTONIC SODIUM CHLORIDE.

Caution should be exercised because of the risk of sodium and water retention when used with corticosteroids and carbenoxolone due to its sodium content.

Additional information on special populations:

No data are available.

Pediatric population:

No data available.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C

Women with childbearing potential/Contraception
There is no adequate experience with the use of isotonic solution of sodium chloride in pregnant women.

Studies on animals are insufficient in terms of effects on pregnancy / and / or / embryonal / fetal development / and / or / birth / and / or postnatal development. (See section 5.3). Potential risk for human is unknown.

PF 0.9% ISOTONIC SODIUM CHLORIDE should not be used during pregnancy unless it is necessary for life-threatening conditions.

Pregnancy

Animal reproduction studies have not been conducted with sodium chloride containing solutions. It is also not known whether PF 0.9% ISOTONIC SODIUM CHLORIDE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

PF 0.9% ISOTONIC SODIUM CHLORIDE should be given to a pregnant woman only if clearly needed.

Delivery:
The effects of PF 0.9% ISOTONIC SODIUM CHLORIDE on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and on the later growth, development, and functional maturation of the child are unknown.

Administration of sodium and dextrose containing solutions during labor and delivery have been reported in the literature. Caution should be exercised, and the fluid balance, glucose and electrolyte concentrations, and acid-base balance, of both mother and fetus should be evaluated periodically or whenever warranted by the condition of the patient or fetus.

Lactation
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PF 0.9% ISOTONIC SODIUM CHLORIDE are administered to a nursing woman.

4.7 Effects on ability to drive and use machines
Driving is not practically possible during infusion of solutions. There is no known effect on driving and the use of machine after it has been used.

4.8 Undesirable effects
Undesirable effects are not expected in normal conditions of treatment. Undesirable effects may result from an excess or deficit of ions in the solution; therefore, frequent monitoring of sodium

and chloride levels is required. The physician should also be alert to the possibility of adverse reactions to drug additives diluted and administered. In such case, prescribing information for drug additives to be administered should be consulted.

Inappropriate administration of intravenous sodium chloride therapy (eg, in patients with heart or kidney failure, during the postoperative period) 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.

If any addition is made to the isotonic solutions to make the solution hypertonic, if the administration is subcutaneous, there may be pain at the injection site.

Sodium accumulation, edema and hyperchloremic acidosis may occur when applied in large volumes.

If an adverse event occurs during administration, the infusion should be stopped, the patient's condition should be evaluated and appropriate treatment measures be started.

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); Not known (cannot be estimated from the available data)

The following adverse effects are those that may result in an excess of sodium or chloride due to overdose, or may be due to administration technique. The frequency of these side effects is not known (it can be seen in as few patients as cannot be identified with the available data).

Blood and lymphatic system disorders
Not known: Thrombosis, hemorrhage

Metabolism and nutrition disorders
Not known: Sodium accumulation, Water retention and edema, Exacerbation of congestive heart failure (due to hypernatremia), Hyperchloremic acidosis.

Nervous system disorders
Not known: Headache, dizziness, restlessness, irritation, convulsions, coma and death (dehydration of the brain associated with hypernatremia).

Cardiac disorders
Not known: Tachycardia (associated with hypernatremia).

Vascular disorders
Not known: Hypertension (associated with hypernatremia).

Respiratory, thoracic and mediastinal disorders

Not known: Pulmonary edema, respiratory depression and respiratory arrest (associated with hypernatremia).

Gastrointestinal disorders
Not known: Nausea, vomiting, diarrhea, abdominal cramps, feeling of thirst, decreased salivation (associated with hypernatremia).

Skin and subcutaneous tissue disorders
Not known: Decreased perspiration (associated with hypernatremia).

Musculoskeletal and connective tissue disorders
Not known: Muscle twitching and rigidity (associated with hypernatremia).

Renal and urinary disorders
Not known: Renal failure (associated with hypernatremia)

General Disorders and Administration Site Conditions
Not known: Fever, Fatigue (due to hypernatremia), Pain at the injection site (due to subcutaneous administration of hypertonic solution with additions).

Surgical and medical procedures
Not known: Febrile reactions, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia (adverse effects that can be seen due to the technique of administration).

4.9 Overdose and therapy
Adverse reactions of sodium excess in the body include nausea, vomiting, diarrhea, abdominal cramps, thirst, reduced salivation, lacrimation and sweating, fever, tachycardia, hypertension, renal failure, peripheral and pulmonary oedema, respiratory arrest, headache, dizziness, restlessness, irritability, fatigue, muscular twitching and rigidity, convulsions, coma, and death.

Excess chloride accumulation in the body may cause a loss of bicarbonate with an acidifying effect on body fluids.

In the event of a fluid or solute overload during parenteral therapy, reevaluate the patient's condition and institute appropriate corrective treatment.

Diuretics may be used in the treatment of oedema associated with isotonic expansion and appropriate replacement therapy which will not cause fluid electrolyte imbalance should be applied.

Treatment of hypervolemic hypernatremia requires removal of more sodium than water from the body and diuretic-induced sodium and water loss can only be met by water. The main purpose of the treatment is to normalize the volume and composition of body fluids.

When overdose is related to medicinal products added to the solution infused, the signs and symptoms of over infusion will be related to the nature of the additive being used. In the event of accidental over infusion, treatment should be discontinued and the patient should be observed for the appropriate signs and symptoms related to the drug administered. The relevant symptomatic and supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Intravenous solutions/Solutions affecting electrolyte balance
ATC Code: B05XA03

PF 0.9% ISOTONIC SODIUM CHLORIDE is an isotonic solution, with an approximate osmolarity of 308 mOsm/l.

The pharmacodynamic properties of the solution are those of the sodium and chloride ions in maintaining the fluid and electrolyte balance.

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, cardiac electrophysiology and in 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.

The pharmacodynamic properties of the added drugs are the same as the pharmacodynamic properties of the added drug.

5.2 Pharmacokinetic properties

General properties:
Pharmacokinetic properties of PF 0.9% ISOTONIC SODIUM CHLORIDE are those of its components (sodium and chloride).

Absorption:
Active substances in drugs administered intravenously reach their maximum plasma concentrations immediately after administration.

Distribution:
Sodium distribution varies according to tissues: it is fast in muscles, liver, kidney, cartilage and skin; it is slow in erythrocytes and neurons; it is very slow in the bone.
Chloride is mainly distributed in extracellular fluids.

Biotransformation

The half-life after radioactively labeled sodium ($_{24}Na$) injection is 11-13 days for 99% of injected sodium and one year for the remaining 1%.

Chloride closely monitors sodium metabolism and changes in the acid-base balance of the body are reflected by changes in chloride concentration.

Elimination:

Sodium is excreted primarily by the renal route, but at the same time the vast majority is reabsorbed by the renal route. A small amount of sodium is excreted with feces and sweat.

Since chloride metabolically monitors sodium, it is mainly excreted by the renal route but also in lesser amounts in feces and sweat.

Linearity/Non-linearity:

Electrolytes in the PF 0.9% ISOTONIC SODIUM CHLORIDE composition show a linear pharmacokinetic behavior when administered to the body at therapeutic doses to complete their deficiency.

5.3 Preclinical safety data

Because the components of the solution are physiological components of human and animal plasma and are not expected to show toxic effects in clinical practice, studies with PF 0.9% ISOTONIC SODIUM CHLORIDE have not been performed to evaluate the effects of carcinogenic, mutagenic potential and fertility.

The safety of medications added into the solution must be considered separately.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for injection

6.2 Incompatibilities

Incompatibility of the medicinal product to be added with the solution must be assessed before addition. In the absence of compatibility data, this solution must not be mixed with other medicinal products.

It is the responsibility of the physician to judge the incompatibility of an additive medication with the solution by checking for eventual color change and/or eventual precipitate, insoluble complexes or crystals apparition. The prescribing information of the drug to be added to PF 0.9% ISOTONIC SODIUM CHLORIDE must be consulted to decide whether the additive is compatible.

Before adding a drug, its solubility and stability at the pH of PF 0.9% ISOTONIC SODIUM CHLORIDE should be verified.

PF 0.9% ISOTONIC SODIUM CHLORIDE should be immediately used following the addition of a compatible drug. Those additives known to be incompatible should not be used.

6.3 Shelf Life
48 months

Shelf life during use for dilution:
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of container
500 ml and 1000 ml glass bottles.
Product has two forms; with and without set.

6.6 Special precautions for disposal and other handling

Unused products or product wastes should be discarded in accordance with the local regulations.

7. MARKETING AUTHORISATION HOLDER
POLİFARMA İLAÇ SAN. VE TİC. A.Ş.
Vakıflar OSB Mahallesi, Sanayi Caddesi, No:22/1, Ergene/Tekirdağ/TURKEY
Tel: +90 282 675 14 04
Fax: +90 282 675 14 05

8. MARKETING AUTHORISATION NUMBER

176/98

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorization: 17.01.1996
Date of renewal of the authorization: 18.08.2016

10. DATE OF REVISION OF THE TEXT
28.11.2019

Directions for use

Solution should be inspected visually before use.
The administration is by intravenous route with sterile, apyrogen sets.

Only products that are clear, particle-free and intact in packaging integrity should be used.

The administration should be started as soon as possible after the application set is attached to the product.

In order to prevent an air embolisation that may occur due to the residual air in the bottle, no serial connection should be made with other infusion fluids.

The solution should be applied using the aseptic technique through the sterile application set. In order to prevent air from entering the system, liquid must be passed through the application set before use.

Additional medication may be added before and during infusion with the aid of Injection a needle in aseptic conditions. The final product's isotonicity should be determined before parenteral administration.

The added drug must be completely mixed with the solution before application to the patient. Solvents containing additional drug should be used immediately after drug addition; it should not be stored for later use.

Addition of additive or wrong application technique may result in a fever reaction due to pyrogen contamination of the product. If an adverse reaction occurs, the infusion should be terminated immediately.

For single use only.
Do not store partly used solutions.
Do not reconnect partly used bottles to the administration systems.

Addition of additional drug:
Attention: As with all parenteral solutions, all substances to be added to the product must be compatible with the product. If an addition is to be made, compatibility should be checked in the final mixture before administration to the patient.

Adding medication before administration
1. Stopper of the bottle is disinfected.
2. Inject the drug to be added to the bottle by using syringe with 19 to 22 gauge needle.

3. Mix the solution and the added drug thoroughly.
Attention: Do not store the bottles which mixed with additional medication.

Adding medication during administration
1. Close the clamp.
2. Stopper of the bottle is disinfected.
3. Inject the drug to be added using syringe with 19 to 22 gauge needle.
4. Remove the solution from the hanger and invert.
5. In this position, tap gently the bottle to allow mixing of solution and medication.
6. Return the bottle to its former position and open the clamp and continue administration.