

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

POLIFLEKS 100 mg/ml Dextran 40 9 mg/ml Isotonic Sodium Chloride Solution for I.V. Infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Active ingredients:

In each 100 ml solution:

Dextran (average molecular weight 40.000): 10 g

Sodium chloride: 0.9 g

#### Excipients:

See section 6.1 for excipients.

Ion concentrations of the solution:

	mmol/liter	mEq/liter
Sodium	154	154
Chloride	154	154

### 3. PHARMACEUTICAL FORM

Sterile and apyrogen solution for intravenous infusion.

Clear, colorless solution.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic indications

- In cases where capillary circulation slows down (shock, burns, fat emboli, pancreatitis, peritonitis and paralytic ileus).
- Arterial and venous circulation failures (gangrene threat, leg ulcers, Raynaud disease, non-hemorrhagic cerebral vessel diseases, and prophylaxis of the thromboembolic events seen after trauma).
- In vascular surgery and plastic surgery (in order to correct the peripheral circulation and to decrease thrombosis probability in inoculated graft).
- In open heart surgeries (in addition to the perfusion liquid used in heart – lung device).

#### 4.2. Posology and method of administration

##### Posology / Frequency and period of administration

It is used as intravenous infusion. The speed of the infusion and the dose to be administered are arranged depending on the clinical progress of the disease.

In cases where capillary circulation slows, such as shock:

- The total dose should not be over 20 ml/kg in the first 24 hours at the beginning. Of this dose, 10 ml/kg part is infused slowly, the remaining part slowly. The daily doses of 10 ml/kg are administered for at most 5 days in the following days.

In cases where arterial and venous circulation fails:

- 500 – 1000 ml is administered per kilogram in the first 24 hours in the beginning. In addition, 500 ml more is administered in the next day and then every other day for at most 2 weeks.

Prophylaxis of the thromboembolic events seen after surgery and trauma:

- 500 – 100 ml (10 – 20 ml per kilogram) is administered through intravenous infusion. Infusion should be started during the surgery or just after the trauma. The cure may be completed by administering 500 ml more in the next day.
- In cases where the thrombosis danger is very much (femur head fracture, malign cases in the abdominal cavity or prostate, for the patients laying down for a long time, for the patients having thrombosis in anamnesis etc.), the treatment is started with 500 – 1000 ml as above. 500 ml more is administered in the next day and then every other day for at most two weeks.

Vascular surgery and plastic surgery:

- 500 ml is administered (approximately 10 ml/kg) through intravenous route during surgery. 500 ml more is administered after the surgery. 500 ml more is administered in the day after the surgery and then every other day for at most two weeks.

Open-heart surgeries:

- It is added to the perfusion liquid about 10 – 20 ml per kilogram. The dextran concentration in the perfusion liquid should not be more than 3%. The dose recommended for after surgery is the same with the one recommended for “cases where capillary circulation slows”.

### **Route of administration:**

Administration is made through intravenous route from peripheral or central veins by means of sterile apyrogen sets (it is used by adding to the perfusion liquid in the open heart surgeries).

In cases where there is the possibility that blood flow is excessively loaded, infusion should be applied slowly.

See Chapter 6.6 for the details related with the application.

### **Special populations:**

#### **Renal/ hepatic impairment:**

It should be applied with care for the patients having failure in the kidney functions; it may be required that the dose is adjusted.

There is no special knowledge about its usage in case of liver failure.

### **Paediatric population**

The dose to be administered and infusion speed is set by the doctor depending on the weight of the patients or the body surface area, clinic and biologic condition and the treatment applied together.

### **Geriatric population**

In general, dose should be selected with care for the elderly patients.

For elderly, it is recommended that the treatment is started with the doses at the bottom of the dose range by considering that the liver, kidney or cardiac functions decreased, other medicines may be used together too or there may be diseases other than the condition tried to be treated.

### **4.3. Contraindications**

It is contraindicated in cases below:

- In case of excessive sensitivity against dextran,
- The ones having apparent homeostatic failure (thrombocytopenia, hypofibrinogenemia etc.) and serious bleeding sickness,
- Apparent heart failure,
- Serious kidney failure progressing with oliguria or anuria.

### **4.4. Special warnings and precautions for use**

A careful clinical monitoring is required at the beginning of all intravenous infusions.

The applications should be conducted under a regular and careful surveillance. Clinical and biological parameters, especially the serum electrolyte levels should be monitored.

Application of intravenous solutions may cause dilution in the serum electrolyte concentration, excessive hydration, congestive conditions, or liquid and/or solute loading such that pulmonary edema is formed. Dilution risk is inversely proportional to the electrolyte concentration. The risk that congestive conditions which may cause peripheral and pulmonary edema develop is directly proportional with the electrolyte concentration in the solution.

The ion concentration of the solution is as below:

	mmol/liter	mEq/liter
Sodium	154	154
Chloride	154	154

The solutions containing sodium must be used carefully in cases of hypertension, congestive heart failure, peripheral or pulmonary edema, or failed kidney functions, preeclampsia condition, aldosteronism condition, or other conditions and treatments (e.g. corticosteroid treatment) progressing with sodium accumulation.

When applying Polifleks dextran 40 to the patients to whom sodium limitation is applied, it should be considered that the solution contains 154 mEq sodium per liter.

Since Polifleks dextran 40 is a hyperoncotic solution, it should be avoided that the vein system is over loaded especially in hidden or apparent heart failure conditions. In cases where infusion is made fast, the volume of the plasma, temporarily, may go up two times of the volume of the liquid given by infusion depending on a gram of dextran holding 20 – 25 ml water. The total dose and infusion speed must be determined depending on the clinical condition of the patient and when required, the arterial blood pressure and central vein pressure of the patient must be monitored.

When Polifleks dextran 40 is treated to the patients dehydrated, the water and electrolyte balance of the patient must be corrected with crystalloid solutions. During the Polifleks dextran 40 treatment, when oliguria, indicating itself with viscous urine is seen, diuresis must be started with crystalloid solutions. If oliguria continues in spite of this, diuretics such as furosemide or mannitol must be used.

The solutions containing dextran must be used with care for the patients with diabetes mellitus.

Since it is known that serious side effects may develop in the early periods of dextran administration, the patients must be monitored carefully in the first minutes of infusion. It should be carefully investigated whether serious hypotension is due to shock or dextran usage or not.

In order to minimize the incompatibility risk with any other medicine to be added to the solution, it must be checked whether there is any blurriness or precipitation in the final mixture infusion of which will be made just after the mixing procedure, before the administration and in certain intervals during the administration.

If the administration will be made with a controlled infusion pump, care should be given that the operation of the pump is stopped before the bag is fully emptied, otherwise air emboli may occur.

The solution is administered through intravenous route by means of sterile sets. It is recommended that the sets used in the intravenous administration are replaced once 24 hours.

Use only if the solution is clear and package and caps are solid.

#### Warnings and precautions related with usage with elderly:

- In general, the dose must be selected carefully for elderly. It is recommended that the treatment is started with the doses at the bottom of the dose interval by considering that the liver, kidney or cardiac functions decreased in the elderly, that other medicine is used together or there may be sicknesses other than the one tried to be treated.

#### **4.5. Interaction with other medical products and other interaction ways**

Some medicines or solutions added to the solution may be incompatible. Like for all parenteral solutions, the incompatibility with additional medicines must be evaluated by the doctor before usage.

If other materials will be added to the solution, aseptic method must be used and rinsed until it is mixed. It must be ensured that there is no color change; undissolved particles and crystallization after the medicines are added inside the solution.

When the solution is used together with corticoids/steroids and carbenoxolone, related with the sodium it contains, care must be given because of the sodium and water retention.

In case that Polifleks dextran 40 is administered together with heparin, there is hemorrhage risk in question.

Dextran 40 infusion doesn't affect blood type, cross-matching and indirect Coombs tests made afterwards. However, the methods where enzyme is used are affected by dextran 40 infusion. If typology and cross-matching is wanted to be made after Polifleks dextran 40 is started to be administered, saline agglutination and indirect antiglobulin methods must be used. When measurements are made with protolytic enzyme techniques, difficulties may be experienced.

Blood glucose measurements made by sulfur or acetic acid hydrolysis methods after dextran administration may give values higher than normal. The laboratory tests made by using turbidimetric methods may cause pseudo rises. It is recommended to take blood samples before administering dextran for these tests.

There is no risk of interaction with diuretics such as warfarin, digoxin and amyloid, spironolactone, triamterene.

#### **Additional information related with special populations**

No interaction study was made.

#### **Paediatric population:**

No interaction study was made.

#### **4.6. Pregnancy and lactation**

##### **General recommendation**

Pregnancy category: C.

##### **Women of childbearing potential /Contraception**

There is no known adverse effect. There is no need for using any birth control method during the usage of the medicine for the women having child birth potential.

##### **Pregnancy**

There is no adequate data related with usage of dextran in pregnant women.

There is no adequate information about treating pregnant women with Polifleks dextran. It wasn't tested in the reproduction toxicology studies in animals, because of this, if there is clear and absolute need during pregnancy, it must be used.

##### **Lactation**

Because it is not known whether Polifleks dextran 40 is migrated to breast milk or not, decision must be given on quitting the medicine or breastfeeding depending on the mother's need for the medicine.

##### **Reproduction ability / fertility**

There is no adverse effect known.

#### **4.7. Effects on ability to drive and use machines**

It is not practically possible to use vehicles during the usage of the solutions administered through infusion. There is no known effect on vehicle and machine usage after it is used.

#### **4.8. Undesirable effects**

The frequency and density classification of the adverse medicine reaction are as below: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), unknown (it cannot be progressed with the data on hand).

##### **Immune system disorders**

Very rare: Anaphylactic reactions progressing with serious hypotension which may cause death

Unknown: Allergic symptoms (like urticarial, nasal congestion, pressure feeling in the chest, slight hypotension).

##### **Metabolism and nutrition disorders**

Unknown: Electrolyte disorders (edema may be seen depending on the widening of the extracellular water volume and water holding in case of Hyponatremia,

congestive heart failure may become intense. Chloride ions may cause bicarbonate loss when they are infused at big amounts and therefore cause acidifying effect), Hypervolemia\*

### **Gastrointestinal disorders**

Unknown: Nausea, vomit, vomit and involuntary defecation in the patients under anesthesia.

### **Musculoskeletal and connective tissue disorders**

Unknown: Arthralgia.

### **General disorders and administration site conditions**

Unknown: Fever, febrile reactions \*; infection in the injection point\*, venous thrombosis spreading by starting in the injection point\*, fleabite\*, extravasation\*.

\* Depending on the administration method.

Infusion must be stopped when side effects are seen during administration and the condition of the patient must be evaluated and suitable treatment precautions must be taken.

Eye must be kept open that the additional medicines administered by diluting may cause adverse effects too. In such a case, the product information of the additional medicine must be checked.

### **4.9. Overdose and treatment**

The most important risk related with the acute overdose of dextran is hypervolemia. In case of overdose, infusion must immediately stop and the patient must be evaluated again for the liquid and solute load and suitable treatment attempts, including diuretic administration, must be made.

Among the adverse reactions seen based on the sodium redundancy in the body are nausea, vomit, diarrhea, cramps in the abdomen, feeling of thirst, decrease in saliva, tear and sweat amounts, fever, tachycardia, hypertension, renal failure, peripheral and pulmonary edema, respiratory standstill, headache, dizziness, stress condition, irritation, weakness, twitching and hardening in the muscles, convulsions, coma, and death.

Excessive chloride accumulation in the body may cause bicarbonate loss and drift to the acidic side in the body fluids.

If overdose depends on the medicines added to the solution, the symptoms and indications based on overdose depend on the properties of the medicine added. If overdosed by accident during treatment, the administration must be ended and the patient must be monitored with regards to indications and symptoms related with the medicine administered. If required, symptomatic and support treatments must be applied.

## 5. PHARMACOLOGICAL PARTICULARS

### 5.1 Pharmacodynamics properties

**Pharmacotherapy group:** ones used instead of blood and plasma protein fractions

**ATC code:** B05AA05

Polifleks dextran 40 is 10% solution of dextran, the average molecular weight of which is 40,000, in isotonic sodium chloride solution. The dextran in the composition consists of the dextran (glucose polymers) with small average molecular weight (40,000), derived from the fermentation of sucrose.

The biological characteristics of dextran depend on the average molecular weight, distribution of molecular weight and molecular structure. The average molecular weight, distribution of molecular weight and molecular structure of dextran 40 are arranged such that blood flow both in general and in the microcirculation is eased and also the plasma volume is rapidly widened.

The basic effect of dextran 40 is that it increases the plasma volume just after it is administered by intravenous route. The fluid in the interstitial region goes back to the intravascular region as a result of colloidal osmotic effect of the preparation. The time and amount of the widening in the maximum plasma volume depend on the volume of dextran 40, plasma volume before administration and renal discharge speed of dextran 40.

Dextran 40 has antithrombotic properties.

Dextran 40 infusion doesn't affect blood type, cross-matching and indirect Coombs tests made afterwards. However, the methods where enzyme is used are affected by dextran 40 infusion.

Sodium is the main cation of the extracellular fluid. It is in the distribution and balance of the fluids in the organism. The changes seen in the liquid volume of the body are generally related with losing sodium from the body or holding sodium in the body.

The organism tries to maintain the fluid volume in the plasma and tonus by arranging that the sodium is put out with urine through antidiuretic hormone of hypophysis. Sodium, in addition to this, is an ion which has a role in maintaining the acid-base balance in the organism together with chloride and bicarbonate ions.

Ions like sodium pass the cell membrane by using various transportation mechanisms such as sodium pump (Na-K-ATPase). Sodium has an important role in neurotransmission, cardiac electrophysiology and renal metabolism.

Chloride is the main anion of the extracellular fluid and closely related with plasma levels and sodium concentration. Changes in the chloride concentration are usually seen in the anomalies in the sodium metabolism. There is also chloride loss together with sodium in the body fluids.

## **5.2. Pharmacokinetic properties**

### **General properties**

The pharmacokinetic properties of Polifleks dextran 40 consist of the properties of the components (sodium, chloride and dextrane).

#### Absorption:

The active ingredients inside the medicine administered through intravenous route reach the maximum plasma concentrations just after administration.

#### Distribution:

Sodium distribution changes depending on the tissues: it is fast in the muscles, liver, kidney, cartilage, and skin, slow in erythrocyte and neurons, and very slow in bones.

Chloride mainly distributed in the extracellular fluids

Dextran mainly stays in the vein. After the intravenous infusion, the dextran molecules with a molecular weight of 50,000 and below are discharged without changing through kidneys. The dextran molecules with a molecular weight of 50,000 and over are metabolized slowly to glucose.

#### Biotransformation:

After the sodium ( $^{24}\text{Na}$ ), marked radioactively, injection, the half-life is 11 – 13 days for 99% of the sodium injected and one year for the remaining 1%.

Chloride closely follows the sodium metabolism and changes occurred in the acid-base balance of the body are reflected with the changes occurred in the chloride concentration.

60% of the dextran is discharged through kidneys within the 6 hours following the dextran 40 infusion, about 70% within 24 hours. 70 mg per kilo of the remaining dextran is burnt by the body within 24 hours.

#### Elimination:

Sodium is mainly eliminated through renal route but at the same time a big majority is re-absorbed through renal route. A small amount of sodium is eliminated by feces and sweat.

Chloride, because it follows sodium metabolically, is mainly eliminated through renal route, a small amount through feces and sweat.

Dextran primarily is eliminated by urine. Small amount of dextran is released to gastrointestinal system and eliminated with feces.

### Linearity / non-linear condition:

The electrolytes in the composition of Polifleks dextran show a linear pharmacokinetic action when they are administered in a ratio completing the lack of the body, i.e. in therapeutic doses.

### **5.3. Pre-clinic reliability data**

Because sodium and chloride, of the components of solution, are physiological components of human and animal plasma and because it is not expected to see toxic effects in case of clinic application, no study was made to evaluate the carcinogen, mutagen potential and its effects on fertility.

Polifleks dextran 40 wasn't tested in toxicology studies in animals. The similar products containing dextran has no teratogen and carcinogen effect, published.

The reliability of the medicine added in the solution must be considered separately.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Water for injection

### **6.2. Incompatibilities**

The blood glucose measurements may give values higher than normal, which made with sulfuric acid or acetic acid hydrolysis method after Polifleks dextran 40 administration. The laboratory tests made by using turbidimetric methods may cause pseudo rises. It is recommended to take blood samples before administering dextran for these tests.

The incompatibility of the medicine to be added to the solution must be evaluated beforehand. In cases where there is no incompatibility data, no medicine must be added to the solution.

Deciding whether the medicine added is incompatible or not by checking whether there is color change and/or precipitation, undissolved components or crystallization or not after the medicine is added is the responsibility of the doctor making the application. It must be decided whether the medicine to be added to Polifleks dextran 40 is incompatible or not by using the prospectus of the medicine to be added.

It must be verified that it is soluble and stable inside Polifleks dextran 40 before adding medicine to the solution.

Polifleks dextran must be used just after a compatible medicine is added inside.

The medicine known to be incompatible must not be added.

### **6.3. Shelf life**

36 months.

Shelf life after medicine is added inside: microbiologically it must be used just after it is prepared for administration. In cases where it is not used immediately, determining the storage condition and time is the responsibility of the one who made medicine addition/dilution and the time; in cases where this procedure is not made validated aseptic conditions, is not normally longer than 24 hours between 2-8°C

### **6.4. Special precautions for storage**

There is no special storage condition. It must be stored in a place in room temperature under 25°C, not directly seeing sun. It must not be frozen.

### **6.5. Characteristics and content of the package**

100, 150, 250, 500 and 1000 ml PVC and PP bag

The product has two forms as with or without set.

### **6.6. Demolition of the materials remained from human medical products and other special precautions**

#### **Usage directive**

The solution must be checked before usage. Only clear products without particles and the package integrity of which is not damaged must be used.

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

In order to prevent air emboli which may occur depending on the remained air in the bag, no serial connection must be made with other infusion liquids.

The solution must be administered by using aseptic technique through sterile administration set. Liquid must be passed before usage from the administration set for air not entering the system.

Additional medicines may be added before and during infusion by means of a needle from the injection edge under aseptic conditions. The isotonicity of the final product formed must be determined before parenteral administration is made.

It is required that the medicine added is completely mixed with the solution before administering the patient. The solutions containing additional medicine must be used just after the medicine is added. It must not be stored for using afterwards.

Adding additional medicine to the solution or wrong administration technique may cause fever reaction based on pyrogen contamination. Infusion must be stopped immediately if adverse reaction is seen.

It is for single usage. **Partially used solutions must not be stored.**

The partially used bags must not be connected to the systems applied to patient again.

**To open:**

1. Check the solidity of the external package and whether there is leakage or not; if the package is damaged, don't use.
2. Open the protective external package by tearing.
3. Check whether the bag inside the protective package is solid or not by squeezing. Check the clearness of the solution inside the bag and whether it contains foreign substances or not.

**Application preparations:**

1. Hang the bag.
2. Remove the protective cover at the administration edge.
3. Tightly insert the spike of the administration set to the administration edge.
4. The usage directive of the set should be followed to administer the solution to the patient.

**Adding additional medicine:**

**Caution:** All substances to be added to the product should be incompatible with the product, like for all parenteral solutions. If adding will be made to the product, the incompatibility should be checked in the final mixture before administering the patient.

***Adding medicine before application***

1. The medicine administration edge is disinfected.
2. The medicine to be added is added inside the bag with an injector which has a needle with a thickness of 19 – 22 gauge.
3. Solution and the medicine added inside is mixed thoroughly. It is ensured that the medicine is mixed by slightly tapping to the administration exit when it is up position for the dense drugs like potassium chloride.

**Attention:** The bags additional drug is applied inside should not be stored.

***Adding medicine during administration***

1. Clamp of the set is closed.
2. The medicine administration edge is disinfected.
3. The medicine to be added is applied from the medicine administration edge with an injector which has a needle with a thickness of 19 – 22 gauge.
4. The solution is removed from the hanger and turned upside down.
5. It is ensured that the medicine is mixed by slightly tapping to the administration exit and injection input of the bag when it is in this position.
6. The bag is brought to the old position; clamp is opened and administration is continued.

**7. MARKETING AUTHORISATION HOLDER**

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**8. MARKETING AUTHORISATION NUMBER(S)**

210/12

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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Renewal Of The Authorisation: 06.03.2014

**10. DATE OF REVISION OF THE TEXT**

12.04.2019