SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Polifleks 20% Mannitol Solution for IV Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredients:
Each 100 ml solution contains 20 g mannitol.

Excipients:
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM
Sterile solution for intravenous infusion.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
POLİFLEKS 20% MANNITOL is a solution with osmotic diuretic effect. It is used for increasing urine exit, decreasing the increased intracranial pressure and intraocular pressure or in cases of intoxication with materials eliminated by renal way, promoting the elimination of these materials from kidneys by preventing oliguria or ensuring its treatment because of the reasons below:

For decreasing the intracranial pressure and brain mass:
- To ease the access to the deeper tissues by surgical method,
- In cases where the intracranial pressure is high, if dura is required to be opened, to prevent brain damage,
- To decrease the increased intracranial pressure and to prevent brain herniation during or before the intervention made for diagnosis,
- To cure secondary brain edema in the postoperative period,
- To decrease cerebrospinal pressure in “pseudotumor cerebri” cases.

For decreasing the increased intraocular pressure:
- To ease the intraocular surgeries,
- To temporarily decrease the intraocular pressure,
- To medically cure some malignant glaucoma cases,
- To decrease surgical risk of malignant glaucoma

For increasing urine exit:

- To prevent transurethral prostate resections in the transfusion or other hemolytic reactions, hemoglobin precipitation in the kidney tubules in burn and other hemoglobinemia cases,
- To increase elimination of uric acid through urine in the patients suffering gout or severe hyperuricemia,
- To correct excessive water loading and hyponatremia depending on this in the patients who don't have organic kidney disease,
- To increase the effect of the diuretics in the patients having edema based on cirrhosis or nephrosis,
- In the discriminative diagnosis of acute kidney failure (anuria) and acute functional oliguria,
- To simplify liquid and electrolyte treatment in oliguria patients.

For preventing oliguria as a result of ischemia depending on the reasons below:

- Clamping abdominal aorta when making aneurysmectomy,
- Extracorporeal circulation made in the cardiotomy or vascular surgery,
- Traumatic and hemorrhagic shock,
- Acute hypertension.

4.2. Posology and method of administration

Posology / Frequency and period of administration

The speed of the infusion and the dose to be administered are adjusted by the doctor depending on the age, weight, clinical and biological condition of the patient and the treatment applied together.

It changes between 250 and 1000 ml per 24 hours for the adults and adolescents. The dose for one time must not be over 250 ml (50 g mannitol). Adequate response is obtained with 250-500 ml daily in most cases (50-100 g mannitol/day).

Normal infusion speed is 30 – 50 ml per hour. 70 ml doses may be applied for 5 minutes in emergencies. After this dose of 5 minutes, infusion must be continued with 30 – 50 ml/hour, which is the normal infusion speed.

The posology below is recommended by considering these general rules, unless otherwise is recommended by the physician:

- For decreasing intraocular and intracranial pressure:

5 – 10 ml solution per kilo (1 – 2 g/kg) is administered intravenously within 15 – 60 minutes. 700 ml may be administered within 30 minutes to an adult patient of 70 kg by this way.

- For discriminating diagnosis of acute renal failure and functional oliguria:

100 ml from the solution is administered intravenously within 5 – 6 minutes, the infusion speed is slowed and a total of 250 ml solution is administered in 45 – 60 minutes. The patient must urinate 50 – 100 ml per hour.

If the urine amount doesn't increase within 1 – 2 hours and the liquid need of the patient is met, a second trial dose may be administered. In spite of this, if diuresis hasn't started in the patient, more than 500 ml (100 g mannitol) must not be administered. Such a persistent oliguria may be a symptom of acute tubular necrosis or chronic pathologic situation in the urogenital system.

After diuresis starts, infusion is continued, if required, by diluting the solution such that 100 ml urinate per hour is ensured. Dextrose or sodium chloride may be added to the solution depending on the metabolic requirement of the patient, liquid and electrolyte balance.

- For decreasing water intoxication and postoperative irrigation during or after transurethral prostate resection or other urogenital surgeries:

A total of 150 ml is given, together with 5% dextrose solution containing with a ratio of 0.48% intravenously for 5 – 10 minutes when anesthesia is started to be applied. By this way, a total of 100 ml liquid is administered at a rate of 300 ml per hour during and after the surgery.

After this, a total of 400 ml is given in an hour with the 5% dextrose 0.2% sodium chloride solution for IV infusion such that 5% dextrose solution containing sodium chloride with a ratio of 0.2% of the ¾ of the solution for 18 hours or until there is no need for irrigation (in this case the ratio of the mannitol in the total liquid becomes 5%).

- To prevent hemoglobin, uric acid and other components hard to dissolve from precipitating to the kidney tubulus and to increase their elimination:

250 ml (50 g mannitol) from the solution to which 40 – 45 milliequivalent sodium lactate or bicarbonate added is administered intravenously in 30 minutes.

After this, a total of 300 – 500 ml is given in an hour with the 5% dextrose 0.2% sodium chloride solution for IV infusion such that 5% dextrose solution containing sodium chloride with a ratio of 0.2% of the ¾ of the solution such that 300 – 500 ml urination is obtained (in this case the ratio of the mannitol in the total liquid becomes 5%).

In order to meet the losses, 40 – 45 milliequivalent sodium lactate and adequate amount of potassium must be added to each liter of the solution, it must be checked whether an adequate alkalization is provided or not by frequently checking the pH of the urine.

- To increase the elimination of barbiturate and other materials present in toxic amounts in the blood:

250 ml (50 g mannitol) from the solution to which 40 – 45 milliequivalent sodium lactate or bicarbonate added is administered intravenously in 30 minutes.

After this, it is continued by giving a total of 300 – 500 ml in an hour with the 5% dextrose 0.2% sodium chloride solution for IV infusion such that 5% dextrose solution containing sodium chloride with a ratio of 0.2% of the ¾ of the solution such that 300 – 500 ml urination is obtained until the barbiturate level in the blood is not toxic. 40 – 45 milliequivalent sodium lactate and 20 milliequivalent potassium chloride and 1 g calcium gluconate must be added to each liter of the solution, it must be checked whether an adequate alkalization is provided or not by frequently checking the pH of the urine.

- To regulate hyponatremia in water intoxication cases:

100 ml is administered intravenously within 5 – 10 minutes and infusion is continued by the rate of 100 ml per hour. The total dose depends on the amount of water required to be eliminated from the body.
1 ml of the solution provides 4 ml urination.

- To clamp extracorporeal circulation, abdominal aorta and to prevent oliguria in the other big surgeries:

250 ml is administered intravenously within 30 minutes after the anesthesia is started (before clamping aorta).

After this, it is given in an hour with the 5% dextrose 0.2% sodium chloride solution for IV infusion such that 5% dextrose solution containing sodium chloride with a ratio of 0.2% of the ¾ of the solution such that 100 ml urination is obtained during the surgery and after the surgery for 18 hours (in this case the ratio of the mannitol in the total liquid becomes 5%).

- To prevent oliguria after open heart surgeries:

To the blood in the pump, of the 20% mannitol solution, containing 0.2% sodium chloride, it is added with the ratio of 2 g mannitol per kilogram of the patient. It is continued as written in the article above.

- To prevent oliguria in acute hypotension, shock and other situations decreasing renal blood circulation:

Posing recommended for discriminating diagnosis of acute renal failure and functional oliguria must be used.

Route of administration:
The administration is made intravenously with sterile apyrogen sets. Hypertonic solutions must be administered from big veins or preferably a central venous route.

See Chapter 6.6 for the details related with the application.

Special populations:
Renal/ hepatic impairment:
Renal failure:
It should be applied with care for the patients having failure in the kidney functions. In such cases, first of all a test dose must be applied and mannitol administration must be continued only if adequate urine flow is obtained

Liver failure:
There is no special dose recommendation for this patient group because there is no study conducted especially for this population.

Paediatric population:
The efficiency and safety isn't shown for the children under 12.
The dose and infusion speed to be administered to the children over 12 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.

In case of renal failure in children, the test dose to be applied for the first 3 – 5 minutes must be 1 ml per kg of the body weight (200 mg/kg). The treatment dose ranges between 2.5 ml and 7.5 ml per kg of the body weight. This dose may be repeated once or twice with intervals of 4 – 8 hours.

In cases of cerebral or ocular edema, this dose may be given within 30 – 60 minutes like adults.

Geriatric population:
The dose and infusion speed to be administered 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.

The dose is generally changes between 250 ml and 1000 ml, like for the adults, in this population. The dose for once must not be over 250 ml (50 g mannitol). In most cases, adequate response is obtained with 250 – 500 ml daily (50 – 100 g mannitol/day).

Because the renal functions may start to be failing in elderly, this situation must be taken into account before determining the dose.

4.3. Contraindications
It is contraindicated in cases below:
- Existing plasma hyperosmolarity condition,
- Severe dehydration,

- Well settled anuria conditions,
- Severe heart failure,
- Severe lung congestion or pulmonary edema conditions,
- Active intracranial bleeding (except the ones seen during craniotomy),
- In cases where blood – brain barrier is failed,
- Severe mannitol sensitivity cases.

4.4. Special warnings and precautions for use

Administering intravenous solution may cause dilution in serum electrolyte concentration, liquid and/or solute loading such that severe hydration, congestive conditions or pulmonary edema occurs.

Dilution risk is inversely proportional to electrolyte concentration. The risk of developing congestive conditions which may cause peripheral or pulmonary edema is directly proportional with the electrolyte concentration in the solution.

The solution doesn't contain electrolyte. The osmolality is about 1100 mOsm/l.

Care must be given to the patients suffering severe renal failure. In such cases, first of all, a test dose must be applied and administering mannitol must be continued only if adequate urine flow is obtained. Mannitol administration to the patients who have renal disease present beforehand or using medicine with nephrotoxic potential increase the risk of developing renal failure.

In cases of shocks in the patients the renal functions of whom are failed, mannitol must not be used before the liquid-electrolyte deficit is closed.

Because a rapid increase in the volume of extracellular liquid may cause a suddenly developing heart failure, before administering POLİFLEKS 20% MANNITOL, the cardiovascular condition of the patient must be evaluated carefully.

In case that the serum osmolality increases during treatment, mannitol's diuresis effect and effects decreasing intraocular and intracranial pressure may decrease.
The patients must be monitored for renal, cardiac and pulmonary functions during mannitol administration and the treatment must be ended in case of any adverse effect.

The passage of intracellular fluid not containing sodium to the extracellular compartment after mannitol infusion may cause decrease in serum sodium concentrations and worsens the existing hyponatremia condition. Sodium and potassium loss increases with urine.

Mannitol may cause that inappropriate hydration and hypovolemia condition gets worsen by hiding them. Liquid and electrolyte balance must be carefully monitored.

If urine continues decreasing during mannitol administration, existing congestive heart failure may become more severe by mannitol subjecting to accumulation or a latent congestive heart failure may become apparent.

The urine amount, liquid balance, central venous pressure and electrolyte balance (especially serum sodium and potassium levels) must be carefully monitored during treatment.

In order to minimize any incompatibility risk with any other medicine to be added to the solution, it must be checked whether there is any blurriness or precipitation or not in the final mixture to be infused just after the mixing procedure, before the administration and at certain intervals during the administration.

If the administration will be made with a controlled infusion pump, care must be given that the operation of pump is stopped before the bag is completely 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.

4.5. Interaction with other medicinal products and other forms of interaction

The effect of mannitol may increase in case that it is used together with other diuretics. Therefore dose adjustment may be required in case of simultaneous usage.

Mannitol may increase elimination of the medicine eliminated with urine (e.g. lithium and methotrexate). Therefore these medicines may not be adequately responded in case of simultaneous usage.

Simultaneous mannitol administration for the patients using medicine with nephrotoxic potential may cause increase in cumulative toxicity because of changes mannitol may cause in the liquid balance. Therefore the patients using siklosporin simultaneously must be monitored closely for nephrotoxicity.

Even though there is limited information on that it is seen in humans, among the other possible interactions are:

- Interactions with the medicines from aminoglycoside group: the autotoxic effects of these medicines may increase when used with mannitol.
- Interactions with depolarization neuromuscular blocker medicines: increase may be seen in the pharmacological effects of these medicines when used with mannitol.
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- Interactions with oral anticoagulants: the effects of these medicines may decrease by increasing the concentrations of the secondary coagulation factors to the effect of mannitol causing dehydration.
- Interactions with digoxin: (there is digoxin toxicity risk if there is hypokalemia after mannitol treatment).

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C.

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

Women of childbearing potential /Contraception

There is no known adverse effect.

Pregnancy

The studies made on animals are inadequate with regards to the pregnancy /and-or/ embryonic/fetal development /and-or/ childbirth /and-or/ development after birth (see chapter 5.3). The potential risk for humans isn't known.

There is no adequate information on curing pregnant women with POLİFLEKS 20% MANNITOL. 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

It is not known whether this medicine is migrated to breast milk or not. POLİFLEKS 20% MANNITOL must be used with care for mothers breastfeeding since it is known that a lot of medicine migrates to the breast milk.

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

Among the adverse effects which may be seen depending on the administration method are febrile reactions, infection in the point of injection, venous thrombosis spreading by starting at the point of injection or fleabite, extravasation, and hypervolemia.

Very fast infusion of hypertonic solutions may cause local pain and venous irritation. The administration speed must be adjusted depending on patient's tolerance. It is recommended for the administration that the widest peripheral vein and a needle thin as much as possible is selected.

The adverse reactions below are notified in the experiences after marketing. The frequency classification of the adverse medicine reaction is as below:

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), unknown (it cannot be progressed with the data on hand).

Immune system disorders
Very rare: Allergic reactions, anaphylactic shocks

Metabolism and nutrition disorders
Uncommon: Liquid and electrolyte imbalances
Rare: Dehydration, edema

Nervous system disorders
Rare: Headache, convulsion, dizziness / daze condition, increase in intracranial pressure.

Eye disorders
Rare: Blurriness in seeing.

Cardiac disorders
Rare: Cardiac arrhythmias.
Very rare: Congestive heart failure.

Vascular disorders
Uncommon: Hypotension, thrombophlebitis.
Rare: Hypertension.

Respiratory, thoracic and mediastinal disorders
Rare: Pulmonary congestion, pulmonary edema, rhinitis.

Gastrointestinal disorders
Rare: Drying in mouth, thirst, nausea, vomit.

Skin and subcutaneous tissue disorders
Rare: Skin necrosis, urticaria.

Musculoskeletal and connective tissue disorders
Rare: Cramps.

Renal and urinary disorders
Rare: Severe diuresis, osmotic nepherosis, urinary retention.
Very rare: Acute renal failure.

General disorders and administration site conditions
Rare: Tremble, chest pain (similar to angina), fever.
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.

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 and the solution remained in the bag must be stored when required.

4.9. Overdose and treatment
If liquid or solute loading based on severe infusion is seen during parenteral treatment, mannitol infusion must be stopped, the patient must be reevaluated and suitable treatment attempts must be made.
Long duration and very fast infusion of hyperosmotic solutions may cause circulation loading and acidosis. The first symptoms may be headache, nausea and shaking without fever. Then, this condition may turn into confusion, lethargy, convulsions, stupor, and coma.
In this case, the liquid and electrolyte balance is closely monitored and symptomatic and supporting treatment is applied. Hemodialysis may be useful.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: intravenous solutions / solutions making osmotic diuresis
ATC code: B05B / B05BC01

POLİFLEKS 20% MANNITOL is a sterile, stable and apyrogen solution prepared for increasing the osmolality of extracellular fluid and for creating osmotic diuresis for intravenous administration. It does contain no bacteriostatic material.

Mannitol, a carbohydrate, stays in the extracellular area. It pulls the intracellular fluids to extracellular compartment with its osmotic effect.

Under normal conditions mannitol may not pass the blood-brain barrier. Mannitol staying in plasma, due to the osmotic pressure it creates, provides that the extra liquid accumulated in the brain tissue leaves this tissue. By this way, intracranial pressure drops and brain matter shrinks.

Mannitol doesn't pass to the eye. Therefore it decreases the intraocular pressure too by promoting discharge of intraocular liquids.

Mannitol is freely filtered in the kidney glomerulus; less than 10% of the mannitol filtered is reabsorbed in the kidney tubules. Mannitol remained in the kidney tubules prevents re-absorbing of the liquid in the glomerular filtrate and cause diuresis. Because of this affect, it promotes urine formation in case of oliguria/anuria or in the conditions where the person is under the risk of acute renal disorder.

Mannitol, in addition to this, increases the elimination of electrolytes, especially sodium, potassium and chloride too. It also increases the elimination of toxic materials eliminated from kidneys such as aspirin and barbiturate.

5.2. Pharmacokinetic properties

Absorption:

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

Distribution:

Mannitol stays in the blood circulation after intravenous administration; doesn't pass to the tissues.

Biotransformation:

Mannitol isn't subject to biotransformation in the body.

Elimination:

80% of the intravenous dose administered is eliminated without subjecting to a change from the kidneys within three hours. It is freely filtered from glomerulus; its tubular re-absorbing is less than 10% and doesn't have tubular secretion.

Elimination half-life is about 2 hours in adults. The half-life extends in case of renal failure.

5.3. Pre-clinic reliability data

Because mannitol is a material used in patients for a long time and included in pharmacopeia, no study was made for the pre-clinic reliability of POLİFLEKS 20% MANNITOL.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of inactive materials

Water for injection

6.2. Incompatibilities

Because of pseudoagglutination risk, POLİFLEKS 20% MANNITOL must not be used by the same set together with blood or by a set where previously blood was applied. For the same reason, blood administration must not be made with a set which POLİFLEKS 20% MANNITOL was administered.

No medicine must be added to the solution in cases where there is no compatibility data.

The compatibility of any medicine which will be added to the solution must be evaluated beforehand and before adding medicine to the solution it must be verified that it can be dissolved in water and stable at the pH (pH = 4.5-7.0) of POLİFLEKS 20% MANNITOL.

Some of the medicines known as incompatible with intravenous mannitol solutions are below:

- Sefepim
- İmipenem / Silastatin
- Filgrastim

6.3 Shelf-life

2 years.

6.4. Special precautions for storage

It must be stored in room temperature under 25°C.

Even though mannitol solutions are stable chemically, concentrated solutions crystallize at very low temperatures. If there are mannitol crystals in the solution, melt it by heating at a temperature of at most 40°C in a water bath and by rinsing. If there is no complete dissolution in spite of this, the solution must not be used.

6.5. Nature and contents of the container

It is presented in PVC and PP bags of 100, 150, 250, 500 and 1000 ml.
The product has two forms as with or without set.

6.6. Destruction of the residual materials human medicinal product and other special precautions

The solution must be checked before using.

Only the 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)

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