SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Biofleks 20% Mannitol solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each 100 ml solution contains 20 g mannitol.

Excipients:

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection (infusion)

Clear, colourless, sterile.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOFLEKS 20% MANNITOL is an osmotic diuretic solution. It is used for increasing urine output, reducing increased intracranial pressure and intraocular pressure or promote renal excretion of the kidneys in case of poisoning by prophylaxis or treatment of oliguria for following reasons:

The Reduction of intracranial pressure and brain mass:

- To facilitate access to the deeper tissues in surgery
- To prevent brain damage in case of high intracranial pressure if dura needs to be opened
- To reduce increased intracranial pressure and to prevent brain herniation during diagnose
- To treat secondary cerebral edema in postoperative period
- To reduce cerebro spinal pressure in “Pseudotumor cerebri” cases

The reduction of elevated intraocular pressure:

- To facilitate intraocular surgeries

- To reduce the intraocular pressure temporarily
- To treat malignant glaucoma
- To reduce the surgery risk of malignant glaucoma

To increase urine output:

- To prevent hemoglobin precipitation in kidney tubules during transfusion or other hemolytic reactions, transurethral resection of prostate, burns and other hemoglobin emiacases
- To increase urinary excretion of uric acid in patients with gout or severe hyperuricemia
- To regulate fluid over load and hyponatremia in patients without organic kidney disease
- To increase effect of diuretics in patients with edema due to cirrhosis or nephrosis
- In differential diagnosis of acute renal failure (anuria) and acute functional oliguria
- To simplify fluid and electrolyte treatment in oliguric patients

Prevention of oliguria as a result of ischemia due to the following reasons:

- Intervention to abdominal aorta during aneurysmectomy
- Extra-corporeal circulation during cardiotomy or vascular surgery
- Traumatic and hemorrhagic shock
- Acute hypotension

4.2 Posology and method of administration

Posology:

The dosage and rate of administration depends on the age, weight, clinical and biological condition of the patient and concomitant therapy.

The general dose range is 250 ml to 1000 ml/day in a 24 hour period, with a dosage limit of 250 ml (50 g mannitol) on any one occasion for adults and adolescents. In most instances adequate response will be achieved at a dosage of 250 to 500 ml/day (50-100 g mannitol/day).

The normal infusion rate is 30 to 50 ml/hour. Only in emergency situations, the maximum infusion rate can be as high as 70 ml/hour for 5 minutes. After 5 minutes, the infusion rate should be readjusted to normal range of 30-50 ml/hour.

Unless otherwise recommended by physician, the following posology is recommended taking into account the following these general rules:

- In reduction of intracranial and intraocular pressure:

  The usual dose is 5-10 ml/kg bw (1-2 g/kg), infused over 15 to 60 minutes. For example, in an adult patient with a body weight of 70 kg: 700 ml of solution can be administered within 30 minutes.

- In differential diagnosis of acute renal failure (anuria) and acute functional oliguria:

  100 ml of solution may be given intravenously within 5 to 6 minutes. Then infusion rate should be reduced and total of 250 ml solution may be administered over a period as 45-60 minutes. 50-100 ml/hour of urine flow should be obtained.

  If urine output does not increase within 1 to 2 hours and if patient's fluid requirements are not met, a second test dose may be given. However, if diuresis does not start, solution > 500 ml (100 g) should not be given. Such a persistent oliguria may be a sign of an acute tubular necrosis or chronic pathological condition in urogenital system.

  After starting of diuresis, so as to provide 100 ml of urine output per hour, infusion may be continued as diluted if necessary. Solution of dextrose and sodium chloride may be added to the solution, according to the fluid and electrolyte balance and the metabolic requirements of the patient.

- In reduction of the need for postoperative irrigation and water intoxications during or after transurethral prostatic resection or other urogenital surgery:

  The solution may be given intravenously with 5% dextrose solution containing 0.45% sodium chloride over a period of 5 to 10 minutes, total amount of solutions may be 150 ml, while starting to anesthesia. In this manner, totally 1000 ml of solution may be administered according to the administration of 300 ml/hour during and after surgery.

  Then, the solution may be administered with “5% Dextrose 0.2% Sodium Chloride Injectable Solution”, 3/4 of this mixture should be 5% dextrose solution containing 0.2% sodium chloride, over a period of 18 hours or until there is no need for irrigation, totally 400 ml of solution per hour may be given (in this manner concentration of mannitol in total fluid is 5%).

- To prevent precipitation in kidney tubules and increase excretion of hemoglobin, uric acid and other compounds that poorly soluble:

  An infusion of 250 ml (50 g mannitol) containing 40 to 45 mEq sodium lactate or bicarbonate may be administered over a period of 30 minutes.

Then, the solution may be administered with "5% Dextrose 0.2% Sodium Chloride Injectable Solution", 3/4 of this mixture should be 5% dextrose solution containing 0.2% sodium chloride, 300 to 500 ml of solution may be given per hour according to provide an urine output as 300 to 500 ml/hour (in this manner concentration of mannitol in total fluid is 5%).

40-45 mEq sodium lactate and sufficient potassium should be added to each liter of solution for the replacement of losses, pH of urine should be checked frequently for alkalinity.

- To promote the urinary excretion of toxins as barbiturates and other substances:

  250 ml (50 g mannitol) solution containing 40 to 45 mEq sodium lactate or bicarbonate may be administered intravenously over a period of 30 minutes. Then, the solution may be administered with "5% Dextrose 0.2% Sodium Chloride Injectable Solution", 3/4 of this mixture should be 5% dextrose solution containing 0.2% sodium chloride, 300 to 500 ml of solution may be given per hour according to provide an urine output as 300 to 500 ml/hour until the concentration of barbiturates decrease to non-toxic level. 40-45 mEq sodium lactate and 20 mEq potassium chloride and 1 g calcium gluconate should be added to each liter of solution, pH of urine should be checked frequently for alkalinity.

- To regulate hyponatremia in case of water intoxication:

  100 ml solution may be given intravenously within 5 to 10 minutes and infusion may be continued as 100 ml/hour. Total dosage depends on the amount of water which desired to remove from the body.

  Each 1 ml of solution provides 4 ml of urine output.

- To prevent oliguria during extracorporeal circulation, intervention to abdominal aorta or other major surgery:

  250 ml solution may be administered intravenously within 30 minutes after starting to anesthesia (before intervention to aorta).

  The solution may be administered with "5% Dextrose 0.2% Sodium Chloride Injectable Solution", 3/4 of this mixture should be 5% dextrose solution containing 0.2% sodium chloride, to provide an urine output as 100 ml/hour (in this manner concentration of mannitol in total fluid is 5%) during and after surgery (up to 18 hours).

- To prevent oliguria after open-heart surgery:

Solution of 20% mannitol containing 0.2% sodium chloride may added to blood in the pump according to 2 g mannitol/kg. Then, administration is continued as indicated above.

- Prevention of oliguria in acute hypotension, shock or other cases which may reduce the renal blood circulation:

  The Recommended posology in differential diagnosis of acute renal failure and functional oliguria should be used.

Method of administration:

Administration is by the intravenous route using sterile equipment. Hypertonic solutions should be administered in a large peripheral or preferably a central vein.

For detailed instructions on the preparation and handling of the product see section 6.6

Additional information on special populations

Renal impairment:

Mannitol should be administered with caution to patients with severely impaired renal function. A test dose should be employed and therapy with mannitol continued only if an adequate urine flow is achieved.

Hepatic impairment:

There are no special dosage recommendations due to absence of specific clinical studies in these patients.

Pediatric populations:

Safety and effectiveness in children below the age of 12 have not been established.

As for adults, the dosage and rate of administration for children > 12 years of age depends on the weight, clinical and biological condition of the patient and concomitant therapy.

In renal insufficiency, the test dose should be 1 ml/kg bw (200 mg mannitol/kg bw) over 3-5 minutes. The treatment dose ranges from 2.5 ml to7.5 ml/kg bw. This dose may be repeated once or twice, after an interval of 4 to 8 hours, if necessary.

For cerebral and ocular oedema, this dose may be given over 30 to 60 minutes as for adults.

Geriatric populations:

As for adults, the dosage and rate of administration depends on the weight, clinical and biological condition of the patient and concomitant therapy.

The general dose range is the same as for adults 250 to 1000 ml/day, with a dosage limit of 250 ml (50 g mannitol) on any one occasion. In most instances adequate response will be achieved at a dosage of 250 to 500 ml/day (50-100 g mannitol/day).

Since incipient renal insufficiency may be present, caution should be used when reviewing patient's status prior to dose selection.

4.3 Contraindications

This solution is contraindicated in patients presenting with:

- Pre-existing plasma hyperosmolarity
- Severe dehydration
- Well established anuria
- Severe heart failure
- Severe pulmonary congestion or pulmonary oedema
- Active intracranial bleeding (except during craniotomy)
- Hypersensitivity to mannitol

4.4 Special warnings and precautions for use

Administration of intravenous solution may cause fluid and/or solute overload which resulting in dilution of serum electrolyte concentrations, excessive hydration, congestive states or pulmonary edema.

Risk of dilution is inversely proportional to the electrolyte concentration. Risk of developing congestive condition that can lead to peripheral and pulmonary edema is proportional to the electrolyte concentration in the solution.

This solution does not contains electrolyte. Osmolarity of the solution is approximately 1100 mOsmol/L.

Mannitol should be administered with caution to patients with severely impaired renal function. A test dose should be employed and therapy with mannitol continued only if an adequate urine flow is achieved. Patients with pre-existing renal disease, or those receiving potentially

nephrotoxic medicinal products, are at increased risk of renal failure following administration of mannitol.

In patients with shock and renal dysfunction, mannitol should not be administered until fluid-electrolytes have been replaced.

The cardiovascular status of the patient should be carefully evaluated before rapidly administering BIOFLEKS 20% MANNITOL since sudden expansion of the extracellular fluid may lead to sudden congestive heart failure.

In case of serum osmolarity increase during treatment, the effects of mannitol on diuresis and reduction of intracranial and intraocular pressures may be impaired.

Patients receiving mannitol should be monitored for any deterioration in renal, cardiac or pulmonary function and treatment discontinued in the case of adverse events.

Shift of sodium-free intracellular fluid into the extra cellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatraemia. Sodium and potassium may be lost in the urine.

Mannitol may obscure and intensify inadequate hydration and hypovolaemia. Fluid and electrolyte balance should be carefully monitored.

Accumulation of mannitol may result if urine output continues to decline during administration and this may intensify existing or latent congestive heart failure.

Urinary output, fluid balance, central venous pressure and electrolyte balance (in particular serum sodium and potassium levels) should be carefully monitored during treatment with mannitol.

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

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

This 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of other diuretics may potentiate the effects of mannitol and dose adjustments may be required.

Mannitol increases the elimination of medicinal products excreted through urine (e.g. lithium and methotrexate) and therefore concomitant use of mannitol may impair the response to these medicinal products.

Concomitant administration of potentially nephrotoxic drugs and mannitol may increase the cumulative toxicity due to fluid imbalance related to mannitol. Therefore, patients receiving concomitant ciclosporin should be closely monitored for signs of nephrotoxicity.

Although there is limited evidence of following interactions occurring in humans, other potential interactions are:

- Aminoglycosides: potentiation of their ototoxic effects by mannitol.
- Depolarising neuromuscular blocking medicinal products: enhancement of their effects by mannitol.
- Oral anticoagulants: mannitol may reduce their effects by increasing the concentration of clotting factors secondary to dehydration
- Digoxin: if hypokalaemia follows mannitol treatment there is a risk of digoxin toxicity.

4.6 Pregnancy and lactation

General advice

Pregnancy Category: C

There are no adequate published data from the use of mannitol in pregnant women.

Women of childbearing potential / Birth control (Contraception):

None stated.

Pregnancy

Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/fetal development/ and-or/ parturition/ and-or/ postnatal development (see 5.3). The potential risk for humans is unknown.

There are no adequate data from the use of mannitol in pregnant women.

Animal reproduction studies have not been conducted with mannitol. Therefore, BIOFLEKS 20% MANNITOL should not be used during pregnancy unless clearly necessary

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 mannitol is administered to a nursing woman

Reproductive ability/fertility:

None stated.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Reactions which may occur because of the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

Too rapid infusion of hypertonic solutions may cause local pain and venous irritation. Rate of administration should be adjusted according to tolerance. Use of the largest peripheral vein and a small bore needle is recommended.

Frequencies used are as follows:

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).

Immune system disorders

Rare: Allergic reaction, anaphylactic shock

Metabolism and nutrition disorders

Uncommon: Fluid and electrolyte imbalance

Rare: Dehydration, oedema

Nervous system disorders

Rare: Headache, convulsions, dizziness, intracranial pressure increased

Eye disorders

Rare: Blurred vision

Cardiac disorders

Rare: Cardiac arrhythmia

Very rare: Congestive heart failure

Vascular disorders

Uncommon: Hypotension, thrombophlebitis

Rare: Hypertension

Respiratory, thoracic and mediastinal disorders

Rare: Pulmonary congestion, pulmonary oedema, rhinitis

Gastrointestinal disorders

Rare: Mouth dry, thirst, nausea, vomiting

Skin and subcutaneous tissue disorders

Rare: Skin necrosis, urticaria

Musculoskeletal and connective tissue disorders

Rare: Cramps

Renal and urinary disorders

Rare: Excessive diuresis, nephrosis osmotic, urinary retention

Very rare: Acute renal failure

General disorders and administration site conditions

Rare: Chills, chest pain (angina-like), fever

The physician should also be alert to the possibility of adverse reactions to drug additives. Prescribing information for drug additives to be administered in this manner should be consulted.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose

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

Prolonged administration or rapid infusion of large volumes of hyperosmotic solutions may result in circulatory overload and acidosis. Headache, nausea and shivering without temperature change may represent initial signs/symptoms. Confusion, lethargy, convulsions, stupor and coma may follow.

Management is symptomatic and supportive, with monitoring of fluid and electrolyte balance. Haemodialysis may be useful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions producing osmotic diuresis
ATC code: B05BC01
BIOFLEKS 20% MANNITOL, is a sterile solution for intravenous administration, prepared for increasing the osmolarity of the extracellular fluid and producing osmotic diuresis. It contains no antimicrobial agents.

Mannitol, a carbohydrate, is confined to the extracellular compartment. It has an osmotic effect, which causes fluid to pass from the intracellular to the extracellular compartment.

Mannitol does not penetrate the blood-brain barrier under usual circumstances. Confined to the plasma, mannitol exerts an osmotic pressure, causing fluid to leave the brain tissue, and brain volume and intracranial pressure to be reduced.

Mannitol does not penetrate the eye. Mannitol promotes excretion of aqueous humour and thereby reduces intraocular pressure.

Mannitol is freely filterable at the kidney glomerulus and less than 10% is reabsorbed back from the kidney tubule. Confined to the kidney tubules, mannitol exerts an osmotic effect, which prevents fluid reabsorption from the glomerular filtrate and produces diuresis. It thereby promotes urine flow in oliguria/anuria or in situations where the patient is at risk of onset of acute renal failure.

Mannitol also increases electrolyte excretion, especially sodium, potassium and chloride. Excretion of renally excreted toxic substances such as aspirin and barbiturates is also increased.

5.2 Pharmacokinetic properties

Absorption:

Intravenous administration results in rapid increases in drug concentration.

Distribution:

Following IV administration, mannitol remains confined to the extracellular compartment; does not cross the tissues.

Biotransformation:

Mannitol is not metabolized in the body

Elimination:

80% of an intravenous dose is excreted unchanged within 3 hours. It is freely filtered by the glomeruli, with less than 10% tubular reabsorption and is not secreted by tubular cells.

The elimination half life in adults is approximately 2 hours, longer where renal failure is present.

5.3 Preclinical safety data

The preclinical safety assessment of BIOFLEKS 20% MANNITOL in animals is not relevant as mannitol is a substance with well established use in patients and is covered by appropriate pharmacopoeial references. The safety of potential additives should be considered separately

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

BIOFLEKS 20% MANNITOL should not be administered simultaneously with, before, or after administration of blood through the same infusion equipment, due to risk of pseudoagglutination.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Compatibility of the medicinal product to be added with the solution must be assessed before addition. Before adding a medicinal product, verify it is soluble and stable in water at the pH of the BIOFLEKS 20% MANNITOL (4.5 to 7.0).

As a guide, cefepime, imipenem, cilastin and filgrastim are incompatible with mannitol solutions.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25 °C

Solutions of mannitol are chemically stable but, concentrated solutions of mannitol may crystallize when exposed to low temperatures. If crystallization occurs, the solution should be warmed by immersing the container in water (up to 40°C) and shaking periodically. If all crystals can not be completely dissolved, the solution should not be used.

6.5 Nature and contents of container

PVC plastic container. It contains either 100 ml, 150 ml, 250 ml or 500 ml of solution in PVC bag with two outputs with protective HDPE Overpouch.

6.6 Special precautions for disposal and other handling

The solution for infusion should be visually inspected prior to use. Use only if the solution is clear, without visible particles and if the container is undamaged.

Administer immediately following the insertion of infusion set.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

Additives may be introduced before infusion or during infusion through the re-sealable medication port. When additive is used, verify isotonicity prior to parenteral administration.

Thorough and careful aseptic mixing of any additive is mandatory. Solutions containing additives should be used immediately and not stored.

Adding other medication or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In case of adverse reaction, infusion must be stopped immediately.

Discard after single use. Discard any unused portion. Do not reconnect partially used bags.

To open:

1. Check the outer packaging for leaks. If the container is damaged, discard the solution.
2. Tear open the protective outer packaging.
3. Check for minute leaks by squeezing the inner bag firmly.
4. If solution is not clear or contains foreign matters, discard the solution

Preparation for administration:

1. Suspend container from eyelet support.

2. Twist off protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Addition of medicinal products:

Caution: As with all parenteral solutions compatibility of the additives with the solution must be assessed before addition.

To add medication before administration:

1. Disinfect medication site.
2. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
3. Mix solution and medication thoroughly. For high-density medication such as potassium chloride, tap the ports gently while ports are upright and mix.

Caution: Do not store bags containing added medications.

To add medication during administration:

1. Close clamp on the set.
2. Disinfect medication site.
3. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
4. Remove container from IV pole and/or turn to an upright position.
5. Evacuate both ports by tapping gently while the container is in an upright position. Mix solution and medication thoroughly.
6. Return container to in-use position, re-open the clamp and continue administration.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

201 / 26

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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Renewal of the authorisatıon: 19 January 2009

10. DATE OF REVISION OF THE TEXT

20 / 11 / 2014