IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0167/037/016
Case No: 2031167

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Baxter Healthcare Limited

Caxton Way, **Thetford**, **Norfolk IP24 3SE**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Mannitol 20% Solution for Infusion BP

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **14/06/2007**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mannitol 20% Solution for Infusion BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mannitol: 200 g/l

Each ml contains 200 mg mannitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Clear, colourless solution, free from visible particles.

Osmolarity: 1098 mOsm/l (approx)
pH: 4.5 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mannitol 20% Solution for infusion is indicated for use as an osmotic diuretic in the following situations:
1. Promotion of diuresis in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established
2. Reduction of intracranial pressure and cerebral oedema, when blood-barrier is intact
3. Reduction of elevated intraocular pressure when it cannot be lowered by other means
4. Promotion of elimination of renally excreted toxic substances in poisoning.

4.2 Posology and method of administration

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

Adults and adolescents:
The general dose range is 250 ml to 1000 ml/day (50 to 200 g mannitol) in a 24 hour period, with a dosage limit of 250 ml (50g mannitol) on any one occasion. In most instances adequate response will be achieved at a dosage of 250 to 500 ml/day (50 to 100g 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 (see also test dose). After 5 minutes, the infusion rate should be readjusted to normal range of 30 to 50 ml/hour.

Patients with marked oliguria or suspected inadequate renal function should first receive a test dose of approximately 1 ml/kg body weight (bw) (200 mg mannitol/kg bw) over a period of 3 to 5 minutes. The response to the test dose is considered adequate if at least 30-50 ml/hour of urine is excreted for 2-3 hours. If an adequate response is not attained, a further test dose may be given. If an adequate response to the second test does is not attained, treatment with mannitol should be discontinued and the patient reassessed as established renal failure may be present.

Reduction of intracranial pressure, cerebral volume and intraocular pressure
The usual dose is 7.5 to 10 ml/kg bw, infused over 30 to 60 minutes. When used preoperatively, the dose should be administered 1 to 1.5 hours before surgery to obtain the maximum effect.

Promotion of elimination of renally excreted toxic substances in poisoning
In induction of forced diuresis in the adjunctive treatment of severe drug intoxications, the dose of mannitol should be adjusted to maintain urinary output of at least 100ml/hour and positive fluid balance of 1-2 litres. An initial loading dose of approximately 125 ml may be given.

Children:
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 to 7.5 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.

Elderly:
As for adults, the dosage 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 (50 to 200 g mannitol in a 24 hour period), with a dosage limit of 250 ml (50 g mannitol) on any one occasion. Since incipient renal insufficiency may be present, caution should be used when reviewing patient's status prior to dose selection.

Administration:
Administration is by the intravenous route using sterile and non-pyrogenic equipment. The administration set should include a filter. Hypertonic solutions should be administered in a large peripheral or preferably a central vein.

4.3 Contraindications

Mannitol 20% Solution for Infusion is contra-indicated 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
- Disturbance of the blood-brain barrier
- Hypersensitivity to mannitol

4.4 Special warnings and precautions for use

Warnings
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 (see Section 4.2).

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic medicinal products, are at increased risk of renal failure following administration of mannitol. Serum osmolal gap and renal function should be closely monitored and appropriate action initiated should signs of worsening renal function appear.

In patients with shock and renal dysfunction, mannitol should not be administered until volume (fluid; blood) and electrolytes have been replaced.

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

The cardiovascular status of the patient should be carefully evaluated before rapidly administering Mannitol 20% Solution for Infusion since sudden expansion of the extracellular fluid may lead to sudden congestive heart failure

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 may be lost in the urine. Mannitol may obscure and intensify inadequate hydration and hypovolaemia.

Urinary output, fluid balance, central venous pressure and electrolyte balance (in particular serum sodium and potassium levels) 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect Inhibition
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.

Cumulative nephrotoxicity of medicinal products due to fluid imbalance related to mannitol
Patients receiving concomitant ciclosporin should be closely monitored for signs of nephrotoxicity.
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) and digoxin (if hypokalaemia follows mannitol treatment there is a risk of digoxin toxicity), although there is limited evidence of such interactions occurring in humans.

4.6 Pregnancy and lactation

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

There are no adequate published data from animal studies with respect to mannitols effect on pregnancy and/or embryo/foetal development and/or parturition and/or postnatal development.

Mannitol should not be used during pregnancy unless clearly needed.

There is no information on excretion of mannitol in breast milk.

Mannitol should not be used during lactation unless clearly necessary.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

	System Organ Class	Symptoms (LLT terms MedDRA 6.1)

Frequency		
Uncommon (>1/1000 - < 1/100)	Metabolism and nutrition disorders	Fluid and electrolytes imbalance
	Vascular disorders	Hypotension
	Vascular disorders	Thrombophlebitis
Rare (>1/10,000 - <1/1,000)	Immune system disorders	Allergic reaction
	Immune system disorders	Anaphylactic shock
	Metabolism and nutrition disorders	Dehydration
	Metabolism and nutrition disorders	Oedema
	Nervous system disorders	Headache
	Nervous system disorders	Convulsions
	Nervous system disorders	Dizziness
	Nervous system disorders	Intracranial pressure increased
	Eye disorders	Blurred vision
	Cardiac disorders	Cardiac arrhythmia
	Vascular disorders	Hypertension
	Respiratory, thoracic and mediastinal disorders	Pulmonary congestion
	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Gastrointestinal disorders	Mouth dry
	Skin and subcutaneous tissue disorders	Skin necrosis
	Gastrointestinal disorders	Thirst
	Gastrointestinal disorders	Nausea
	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders	Urticaria
	Musculoskeletal and connective tissue disorders	Cramps
	Renal and urinary disorders	Excessive diuresis
	Renal and urinary disorders	Nephrosis osmotic
	Renal and urinary disorders	Urinary retention
	General disorders and administration site conditions	Chills
	General disorders and administration site conditions	Chest pain (angina-like chest pain)
	General disorders and administration site conditions	Fever
Very rare (<1/10,000)	Cardiac disorders	Congestive heart failure
	Renal and urinary disorders	Acute renal failure

4.9 Overdose

In case of suspected overdose, treatment with mannitol should be stopped immediately.

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 helpful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: “Solutions producing osmotic diuresis”, ATC code: “B05BC01”
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 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.

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.

5.2 Pharmacokinetic properties

When administered intravenously, mannitol is eliminated largely unmetabolised through the glomeruli. 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. 80% of an intravenous dose is excreted unchanged within 3 hours.

5.3 Preclinical safety data

The preclinical safety assessment of mannitol 20% in animals is not relevant as mannitol is a substance with well-established use in patients and is covered by appropriate pharmacopoeial references.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

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

Incompatibility of the medicinal product to be added with the solution in the Viaflo container must be assessed before addition.

The Instructions for Use of the medicinal product to be added must be consulted.
Before adding a medicinal product, verify it is soluble and stable in water at the pH of the mannitol solution (4.5 to 7.0)

As a guide, cefepime, imipenem, cilastin and filgrastim are incompatible with mannitol solutions, but this list is not exhaustive.

The addition of potassium or sodium chloride to Mannitol 20% may cause precipitation of mannitol.

6.3 Shelf Life

Unopened:
100 ml containers: 2 years
250ml, 500ml and 1000 ml containers: 3 years

In-use shelf life: Additives
Chemical and Physical stability of any additive at the pH of Mannitol solution in the Viaflo container should be established prior to use.
From a microbiological point of view, the diluted 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

Do not refrigerate or freeze.

6.5 Nature and contents of container

The bags, known as Viaflo, are composed of polyethylene/polyamide/ polypropylene co-extruded plastic.

The bags are overwrapped with a protective plastic pouch composed of polyamide/polypropylene.

Bag sizes: 100, 250, 500 or 1000ml.

Outer carton contents:

50	bags of	100ml
30	bags of	250ml
20	bags of	500ml
10	bags of	1000ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following insertion of the infusion set.

Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

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.

Medicinal products may be introduced before infusion or during infusion through the injection site.

In cooler temperatures the mannitol may form crystals. Redissolve any crystallised mannitol by warming in a water bath heated to 50-70^{o}C, agitating the solution vigorously periodically. Cool to 37^{o}C before infusion.

Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

To open
Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution, as sterility may be impaired.

Preparation for administration
1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container
3. Use an aseptic method to set up the infusion.
4. Attach administration set. Refer to complete directions accompanying set.

Techniques for injection of additive medicinal products
Warning: Additives may be incompatible.
To add medicinal products 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

To add medicinal products 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 intravenous pole and/or turn to an upright position.
5. Evacuate both ports by tapping gently while the container is in an upright position.
6. Mix solution and medication thoroughly.
7. 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

PA 167/37/16

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th September 2007

Date of last renewal: 7th December 2007

10 DATE OF REVISION OF THE TEXT

December 2007