IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0179/038/001
Case No: 2035401

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

B. Braun Medical Limited

3 Naas Road Industrial Park, **Dublin 12**, **Ireland**

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

Gelofusine, solution for infusion

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 **14/10/2007**.

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

Gelofusine, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

	per 500 ml	per 1000 ml
Gelofusine contains:		
Succinylated gelatin (modified fluid gelatin)	20.00 g	40.00 g
Sodium chloride	3.51 g	7.01 g
Sodium hydroxide	0.68 g	1.36 g
Electrolytes		
Na^+	77.00 mmol	154.00 mmol
Cl^-	60.00 mmol	120.00 mmol

Physico-Chemical Properties	
Weight average molecular weight (Mw)	30,000 Daltons
Number average molecular weight (Mn)	23,200 Daltons
pH	7.4 ± 0.3
Relative viscosity (at 37^{o}C)	1.9
Iso-electric point	pH 4.5 ± 0.3
Colloid osmotic pressure (at 37^{o}C)	453 mm H_2O
	33.3 mm Hg
Gel point	≤ + 3 ^{o}C
Osmolarity	274 mOsm/l

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless or slightly yellowish, aqueous solution with a pH of 7.1-7.7 and an osmolarity of 274 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a plasma volume substitute for use in the initial management of hypovolaemic shock due to blood or plasma loss, dehydration or peri-operative loss of circulating fluid. The solution can be used for haemodilution and as a priming solution for extracorporeal circulation systems and as a carrier solution for insulin.

In the context of the replacement of specific components following blood loss, it is generally possible to avoid giving red cells until the losses amount to 20% of the total blood volume. If more than 2,000-3,000ml of Gelofusine® are infused pre- and intraoperatively, it is recommended that the serum protein concentration be checked post-operatively, especially if there are signs of tissue oedema.

Under certain circumstances (e.g. septic shock, where there may be a need for specific globulins) a human albumin

preparation may be the appropriate choice for further volume expansion.

4.2 Posology and method of administration

The solution is administered intravenously. Dosage volume, and rate of administration depends upon the individual patient state, circumstances and his response. The duration and quantity of the infusion is to be determined individually on the basis of pulse, blood pressure, peripheral perfusion and diuresis.

As a general guide 500ml may be given in not less than 60 minutes. In severe acute blood loss, 500ml may be infused rapidly until signs of hypovolaemia are improved. Precautions are: Pressure infusion, see section 4.4, Special warnings and Precautions for Use and figures at the end of this text. A maximum of 2 litres in adults or 30ml/kg in children should be exceeded only if blood is unavailable. In such cases, an adequate haematocrit should be maintained, and dilutional effects on coagulation should be avoided.

In case of pressure infusion, all air should be removed from the container using either a vented giving set or the filtered venting needle provided.

If there is blood/fluid loss in excess of 1.5 litres in the adult (i.e. greater than 20% blood volume) blood should usually be administered as well as Gelofusine®. The haemodynamic, haematological and coagulation systems should be monitored.

(The haematocrit should not fall below 25% or in elderly patients better not below 30%, and coagulation disorders caused by dilution should be avoided).

4.3 Contraindications

Use in uncontrolled congestive cardiac failure or in circulatory overload.
Known hypersensitivity to the active constituent.

4.4 Special warnings and precautions for use

Allergic reactions of varying severity may occur due to histamine release. Their frequency and severity is reported as being greater in atopic patients. Immediate resuscitative measures should be available.

Treatment:
The Gelofusine® infusion should be stopped immediately. Further treatment depends on the severity of the anaphylactoid reaction:

- Alternative volume replacements.
- Elevation of the legs.
- Administration of oxygen.
- Immediate administration of adrenaline/epinphrine parenterally (e.g. 0.5-1 ml of adrenaline/epinephrine 1:1,000 intramuscularly,
  repeated if necessary, every 15 minutes or 5-10 ml of adrenaline/epinephrine 1:10,000 slowly intravenously).
- Administration of high-dose corticosteroids intravenously.
- Antihistamines (e.g. chlorpheniramine 10-20 mg slowly intravenously).
- Calcium (caution in patients being treated with cardiac glycosides) intravenously may be necessary.
- Observations and treatment of the metabolic acidosis.

Gelofusine ® should only be used with extreme caution in patients with serious cardiovascular disorders (including hypertension, congestive heart failure, cardiogenic shock), pulmonary functional impairment, renal failure, haemorrhagic diatheses or sodium or potassium deficiency. Careful and appropriate monitoring should accompany administration.

Gelofusine ® should not be used to correct drug-induced hypotensive effects.

In case of pressure infusion, which might be necessary in vital emergencies, all air must be removed from the container and the infusion set before the solution is administered.

4.5 Interaction with other medicinal products and other forms of interaction

Although water soluble drugs may be given in Gelofusine ®, experience is limited. Electrolyte and carbohydrate solutions may be given together through the same cannula as the Gelofusine® solution but this is not permitted for fat emulsions.

During Gelofusine® infusions the results of the following clinical chemistry tests may be unreliable:

- Blood sugar.
- ESR.
- Specific gravity of urine.
- Protein.
- Biuret.
- Fatty acids.
- Cholesterol.
- Fructose.
- Sorbitol dehydrogenase.

The low calcium content does not give rise to clotting in the giving set when citrated blood precedes and/or follows administration.

4.6 Pregnancy and lactation

There is very little information available on the use of plasma substitutes in pregnant or lactating women. No embryotoxic effect has, however, hitherto been observed, but there is a small risk of severe anaphylactoid reactions.

As with all drugs, the benefits and risks of use should be assessed in the light of the patients condition: Under these circumstances this preparation should only be prescribed when the potential advantage outweighs the potential risk to the foetus.

Gelofusine® may be used in the initial treatment of blood loss during pregnancy where plasma volume replacement is needed.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Anaphylactoid / anaphylactic reactions can occur as a result of Gelofusine® administration (see 4.4 Special warnings and precautions).

4.9 Overdose

Gelofusine ® should be given with care to patients who are susceptible of circulatory overloading (e.g. severe congestive cardiac failure or renal failure with oliguria or anuria) since excessive volumes may give rise to circulatory overload and electrolyte imbalance.

Treatment:
The infusion should be stopped and the patient treated symptomatically. Electrolytes should be monitored. If necessary

a diuretic may be given to promote fluid loss.

Decreased urinary output secondary to shock is not a contraindication unless there is no improvement in urine output after the initial dose of Gelofusine ®.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isotonic sterile and pyrogen-free 4% solution of succinylated gelatin in 0.9% NaCl. It has a volume effect comparable to the volume infused, and therefore does not have an intrinsic volume expander effect.

The infusion of Gelofusine® increases the plasma volume. This produces an increase in venous return, cardiac output, arterial blood pressure and peripheral perfusion. The osmotic diuresis induced by Gelofusine® has a substantial effect on the maintenance of renal function in shock.

The combination of the following effects of a Gelofusine® infusion produces an improved oxygen supply to the tissues:

- Haemodilution with Gelofusine®, which has a relative viscosity similar to plasma, reduces the relative viscosity of the blood. When given in the initial management of hypovolaemic shock the overall result is a considerably improved pattern of blood flow with an increased cardiac output.

- The Gelofusine® infusion reduces the haematocrit and thereby the oxygen- carrying capacity of the blood. However, the reduction in blood viscosity and the positive changes in the microcirculation reduce the workload of the heart, so that the cardiac output can be increased without any increase in myocardial oxygen consumption. The overall effect of the Gelofusine® infusion, taking into account this increase in cardiac output is to increase the oxygen transport (if the haematocrit doesn't sink below about 25% or in elderly patients better not below more than 30%).

- Furthermore, the colloid osmotic properties of Gelofusine® prevent or reduce the possibility of interstitial oedema, which may limit the oxygen supply to the tissues.

5.2 Pharmacokinetic properties

Gelofusine® has been shown to have a multi-phase elimination curve from the blood circulation, with a half-life of about 4 hours in the first phase and a clear volume effect of about 5 hours.

It appears that some 75% of the infused gelatin molecules are excreted through the kidneys and about 15% in the faeces. In animal experiments retention in the reticulo-endothelial system for 24-48 hours has been demonstrated. The fraction which is not directly excreted is broken down by proteolysis. This breakdown process is so effective that there is no accumulation even in renal failure.

The dose administered is always determined by the goal of an adequate circulation. This applies even when renal excretion is reduced.

5.3 Preclinical safety data

Toxicological investigations with Gelofusine showed it to be well tolerated, so much so that the maximum dosage is limited by the volume infused and its haemodiluting effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Gelofusine has a low calcium content (max 0.4 mmol/1) and therefore will not cause clotting of blood or plasma.

6.3 Shelf Life

Shelf life of the medicinal product as packaged for sale:

3 years.

Shelf life after first opening the container:

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.

Do not use unless the solution is clear and container is intact.
Any unused solution is to be discarded.
Only unopened containers of product should be used.

6.5 Nature and contents of container

Gelofusine is available in the following containers and pack sizes:

1 x 10 semi-flexible polyethylene bottles of 500 ml.

Each box contains 10 filtered venting needles.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

B Braun Medical Limited
3 Naas Road Industrial Park
Dublin 12

8 MARKETING AUTHORISATION NUMBER

PA 179/38/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 October 1992

Date of last renewal: 14 October 2007

10 DATE OF REVISION OF THE TEXT

November 2007