DIRECTIONS FOR USE

340/12612580/0320

Gelofusine®

1. NAME OF THE MEDICINAL PRODUCT

Gelofusine®
Plasma substitute for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of solution contains:

Succinylated gelatine (= modified fluid gelatine) (Molecular weight, weight average: 26 500 Dalton)	40.0 g
Sodium chloride	7.0 g

Electrolyte concentrations

Sodium	154 mmol/l
Chloride	120 mmol/l

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion;
Clear, colourless or slightly yellowish solution.

Physicochemical characteristics

pH	7.4 ± 0.3
Theoretical osmolarity	274 mOsm/l

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gelofusine® is a colloidal plasma volume substitute for
– Treatment of relative or absolute hypovolaemia and shock;
– Prophylaxis and treatment of hypotension
– caused by relative hypovolaemia during induction of epidural or spinal anaesthesia
– due to imminent significant blood loss in a surgical setting;
– Procedures involving extracorporeal circulation as a component of priming fluid in combination with crystalloid solutions (e.g. heart-lung machine);

4.2 Posology and Method of Administration

Posology

Dosage and infusion rate are adjusted according to the amount of blood loss and to individual needs for restoration and maintenance of a stable haemodynamic situation, respectively. The dose administered is initially 500 to 1000 ml on average, in case of severe blood loss higher doses can be applied.

Adults

In adults, 500 ml is administered at an appropriate rate depending on the haemodynamic status of the patient. In the case of more than 20 per cent blood loss usually blood or blood components should be given in addition to Gelofusine® (see 4.4).

Maximum dose:

The maximum daily dose is determined by the degree of haemodilution. Care must be taken to avoid a decrease of haemoglobin or the haematocrit below critical values.

If necessary, blood or packed red cells must be transfused additionally.

Attention must also be paid to the dilution of plasma proteins (e.g. albumin and coagulation factors), which must be adequately substituted if necessary.

Infusion rate:

Up to the first 20 ml of solution should be infused slowly in order to detect anaphylactic/anaphylactoid reactions as early as possible. See also sections **4.4** and **4.8**.

In severe, acute situations, Gelofusine® may be infused rapidly by pressure infusion, 500 ml can be administered 5 – 10 min, until signs of hypovolaemia are relieved.

Paediatric population

The safety and efficacy of Gelofusine® in children have not yet been completely established. Therefore, no recommendation on a posology can be made. Gelofusine® should only be administered to these patients if the expected benefits clearly outweigh potential risks. In those cases the patient's prevailing clinical condition should be taken into account and the therapy should be monitored especially carefully (see section 4.4).

Elderly patients

Caution should be exercised in patients suffering from further diseases like cardiac insufficiency or renal insufficiency that are frequently associated with advanced age. (See section 4.4).

Method of administration

Intravenous use

In cases 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.

4.3 Contraindications

– Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
– Hypervolaemia,
– Hyperhydration,
– Acute congestive cardiac failure
– Severe hypernatraemia
– Severe hyperchloraemia

4.4 Special Warnings and Precautions for Use

Gelofusine® should be administered with caution to patients with a history of allergic diseases, e.g. asthma.

Gelatine preparations for volume replacement may rarely cause allergic (anaphylactic/anaphylactoid) reactions of varying degrees of severity. In order to detect the occurrence of an allergic reaction as early as possible, up to the first 20 ml should be infused slowly and the patient should be under careful observation especially at the beginning of the infusion.

Caution must be exercised in patients suffering from alpha-gal allergy (mammal meat allergy). There is a higher probability that these patients are sensitised to gelatine solution.

In case of an allergic reaction, the infusion must be stopped immediately and appropriate treatment given.

Gelofusine® should only be administered with caution to patients
- at risk of circulatory overload e.g. patients with right or left ventricular insufficiency, hypertension, pulmonary oedema or renal insufficiency with oligo– or anuria.
- with severely impaired renal function
- with oedema with water/salt retention
- with major blood coagulation disorders
- of advanced age as these are more prone to develop disorders such as cardiac or renal insufficiency

As with all colloids, Gelofusine® should only be used if hypovolaemia can not be sufficiently treated with crystalloids alone. In severe hypovolaemia colloids are usually applied in combination with crystalloids.

Volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary or cardiocirculatory problems.

Checks of serum electrolyte concentrations, acid-base balance and water balance are necessary, in particular in patients with hypernatraemia, hyperchloraemia or impairment of renal function.

Electrolytes and fluids should be substituted according to individual requirements if necessary.

The haemodynamic, haematological and coagulation system should be monitored.

During compensation of severe blood losses by infusions of large amounts of Gelofusine®, the haematocrit and electrolytes must be monitored under all circumstances.

Likewise in those situations the dilution effect on coagulation factors should be observed, especially in patients with existing disorders of haemostasis.

Because the product does not substitute lost plasma protein, it is advisable to check the plasma protein concentrations, see also section **4.2**, "Maximum dose".

Paediatric population

There is insufficient experience with the use of Gelofusine® in children. Therefore, Gelofusine® should only be administered to these patients if the expected benefits clearly outweigh potential risks. (See also section 4.2).

Influence on laboratory tests

Laboratory blood tests (blood group or irregular antibodies) are possible after Gelofusine® infusions. Nevertheless it is recommended to draw blood samples before the infusion of Gelofusine® in order to avoid hampered interpretation of results.

Gelofusine® may have an influence on the following clinical-chemical tests, leading to falsely high values:
- erythrocyte sedimentation rate,
- specific gravity of urine,
- unspecific protein assays, e.g. the biuret method.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Caution should be exercised in patients concurrently taking or receiving medicinal products that can cause sodium retention (e.g. corticosteroids, non-steroidal anti-inflammatory agents) as concomitant administration may lead to oedema.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of Gelofusine® in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Due to the limited data available and the possibility of severe anaphylactic/anaphylactoid reactions, with consecutive foetal and neonatal distress, the use of Gelofusine® solutions during pregnancy should be restricted to emergency situations.

Breast-feeding

There are no or limited data regarding the excretion of succinylated gelatine in mother's milk, but because of its high molecular weight it is not expected that the milk will contain relevant amounts. Sodium and chloride are normal constituents of the human body and of food. No significant increase in the content of these electrolytes in mother's milk is expected following the use of Gelofusine®.

Fertility

There are no data on the effect of Gelofusine® on human or animal fertility. However, because of the nature of its constituents it is considered unlikely that Gelofusine® will affect fertility.

4.7 Effects on Ability to Drive and Use Machines

Gelofusine® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

Undesirable effects are listed according to their frequencies 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)

As with other colloidal plasma substitutes, side effects can occur during and after the use of Gelofusine®. These will usually involve anaphylactic/anaphylactoid reactions of varying severity. (See 4.4. Special warnings and precautions for use).

Immune system disorders

Rare: Anaphylactic/anaphylactoid reactions up to shock
In the event of an anaphylactoid reaction, the infusion must be discontinued immediately and the usual emergency treatment given.

Cardiac disorders

Very rare: Tachycardia

Vascular disorders

Very rare: Hypotension

General disorders and administration site conditions

Very rare: Fever, chills

Gastro intestinal disorders

Unknown: nausea, vomiting, abdominal pain

Investigations

Unknown: oxygen saturation decreased

Blood and lymphatic system disorders

Very common:

Decreased haematocrit and reduced concentration of plasma proteins.

Common (depending on the administered dose):

Relatively large doses of Gelofusine® result in dilution of coagulation factors and can therefore affect blood coagulation. Prothrombin time can be increased and activated partial thromboplastin time (aPTT) can be prolonged after administration of large doses of Gelofusine®. See section 4.4.

4.9 Overdose

Symptoms

Overdose of Gelofusine® may cause hypervolaemia and circulatory overload, with a significant fall in haematocrit and plasma proteins, accompanied by an electrolyte and acid base imbalance. This may be associated with consecutive impairment of heart and lung function (pulmonary oedema). Symptoms of circulatory overload are e.g. headache, dyspnoea, and jugular vein congestion.

Treatment

In case circulatory overload appears, the infusion must be stopped and a rapid-acting diuretic should be given. If an overdose occurs, the patient should be treated symptomatically with monitoring of electrolytes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Blood substitutes and plasma protein fractions
ATC code: B05A A06, gelatine agents.

Gelofusine® is a 40 mg/ml solution of succinylated gelatine (also known as modified fluid gelatine) with an average molecular weight of 26 500 Dalton (weight average).

The negative charges introduced into the molecule by succinylation cause an expansion of the molecule. The molecular volume is therefore higher than that of unsuccinylated gelatine of the same molecular weight.

In healthy volunteers, the measured initial volume effect of Gelofusine® was found to be between 80 – 100 % of the infused volume with a sufficient volume effect over 4-5 hours

Gelofusine® does not interfere with the determination of blood groups.

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Mechanism of action:

The colloid-osmotic pressure of the solution determines the extent of its initial volume effect. The duration of the effect depends on the clearance of the colloid mainly by renal excretion. Since the volume effect of Gelofusine® is equivalent to the administered amount of solution. Gelofusine® is a plasma substitute, not a plasma expander

The solution also restores the extravascular compartment, and does not disturb the electrolyte balance of the extracellular space.

Pharmacodynamic effect:

Gelofusine® substitutes intra- and extravascular volume deficits caused by losses of blood, plasma and interstitial fluid. Thus the mean arterial pressure, the left-ventricular end-diastolic pressure, the cardiac stroke volume, the cardiac index, the oxygen supply, the microcirculation and the diuresis are increased without dehydrating the extravascular space.

5.2 Pharmacokinetic Properties

Distribution:

After infusion, Gelofusine® is rapidly distributed in the intravascular compartment.

Biotransformation/elimination:

Most of the infused Gelofusine® is excreted via the kidneys. Only a minor amount is excreted in faeces and not more than about 1 % is metabolised. The smaller molecules are excreted directly by glomerular filtration while the larger molecules are first degraded proteolytically in the liver and secondly are excreted via kidney.

Pharmacokinetics in special clinical situations:

The plasma half-life time of Gelofusine® may be prolonged in patients on haemodialysis (GFR < 0.5 ml/min), however no accumulation of gelatine is observed.

5.3 Preclinical Safety Data

Non-clinical data for the individual components of Gelofusine® reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity. There is no or limited non-clinical data available for reproductive toxicity.

There are no studies on the mutagenic and carcinogenic potential of gelatine.

The maximum dose of the product is limited by its volume and dilution effects, not by any intrinsic toxicological properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium hydroxide(for pH adjustment),
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

-unopened

Bottles of low density polyethylene, 'Ecoflac plus':
Stored below 25°C – 3 years
Stored below 30°C – 2 years
Plastic bags, 'Ecobag' (non-PVC):
2 years

-after first opening the container

The infusion should commence immediately after connecting the container to the giving set.

-after addition of additives

Not applicable (see section 6.2).

6.4 Special Precautions for Storage

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

6.5 Nature of Container

Gelofusine® is supplied in

- Bottles of low-density polyethylene (LDPE), contents: 500 ml, 1000 ml available in packs of 10 x 500 ml, 10 x 1000 ml
- Plastic bags made of a five layer laminate sealed with halogenbutyl rubber stoppers and an outer bag, contents 250 ml, 500 ml, 1000 ml available in packs of, 20 x 250 ml, 20 x 500 ml, 10 x 1000 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

The product is supplied in containers for single-use only. Unused contents of an opened container must be discarded and not be stored for later use. Do not re-connect partially used containers.

Use immediately after connecting container to the giving set.

Only to be used if solution is clear, colourless or slightly yellowish and the container and its closure are undamaged.

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Manufactured by:
B. Braun Medical Industries Sdn. Bhd.
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