SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gelofusine® Ecobag

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1000 ml of Gelofusine Ecobag contains:

Succinylated Gelatin (Modified Fluid Gelatin)	40.0 g
Electrolytes:	
Na+	154.0 mmol
Cl -	120.0 mmol
Physico-chemical properties.	
Weight average molecular weight (Mw)	30 000 Dalton
Number average molecular weight (Mn)	23 200 Dalton
pH	7.4±0.3
Osmolarity	274 mOsm/l

For excipients see 6.1

3. PHARMACEUTICAL FORM

Solution for infusion
A clear, colourless or slightly yellowish aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Gelofusine is a colloidal plasma volume substitute for:

- Treatment of relative or absolute hypovolaemia and shock
- Prophylaxis 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

As with all colloids, Gelofusine should only be used if hypovolaemia cannot 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.

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 the haemoglobin or 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 section 4.4**)**

In severe, acute situations, Gelofusine may be infused rapidly by pressure infusion, 500 ml can be administered in 5-10 minutes, 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 also 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 also section 4.4).

Method of administration

Intravenous use.
Before rapid infusion, Gelofusine may be warmed to not more than 37°C.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. This is to avoid the risk of air embolism that might otherwise be associated with the infusion.

4.3 Contraindications

- Hypersensitivity to gelatin-containing solutions or to any of the excipients listed in section 6.1
- Hypersensitivity to galactose-α-1,3-galactose (alpha-Gal) or known allergy to red meat (mammal meat) and offal (see section 4.4)
- Hypervolaemia
- Hyperhydration
- Acute congestive cardiac failure

4.4 Special warnings and precautions for use

Anaphylactic/ anaphylactoid reactions

Modified fluid gelatin solutions should be administered with caution to patients with a history of allergic diseases, e.g. asthma.
Modified fluid gelatin solutions 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, the first 20 ml should be infused slowly and the patient should be under careful observation especially at the beginning of the infusion. For symptoms of anaphylactoid reactions, see section 4.8.

Due to possible cross-reactions involving the allergen galactose-alpha-1,3-galactose (alpha-Gal), the risk of sensitization and consequent anaphylactic reaction to gelatin-containing solutions could be highly increased in patients with history of allergy to red meat (mammal meat) and offal and/or tested positive for anti-alpha-Gal IgE antibodies. Gelatin-containing colloidal solutions should not be used in these patients (see section 4.3)

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

Risks related to fluid and electrolyte administration

Gelofusine should only be administered with caution to patients

- at risk due to 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 severe hypernatraemia
- with severe hyperchloraemia
- having oedema with water/salt retention
- with major blood coagulation disorders
- of advanced age (elderly patients) as those are more prone to develop disorders such as cardiac or renal insufficiency

Clinical monitoring should include regular checks of serum electrolyte concentrations, acid-base balance and water balance, in particular in patients with hypernatraemia, hyperchloraemia or impairment of renal function. Gelofusine contains supraphysiological concentrations of sodium (154 mmol/L) and chloride (120 mmol/L).

Special attention should be paid to the appearance of symptoms of hypocalcaemia (e.g. signs of tetany, paraesthesia); then specific corrective measures should be taken.

Influence on haemodilution and blood coagulation
The haemodynamic, haematological and coagulation system should be monitored.

During compensation of severe blood losses by infusions of large amounts of Gelofusine, haematocrit and electrolytes must be monitored. The haematocrit should not decrease below 25%. In elderly or critically ill patients it should not fall below 30%.

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 Interaction 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 due to maternal hypotension, the use of modified fluid gelatin 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)		

<u>Summary of the safety profile</u>

Adverse drug reactions can occur during and after the use of Gelofusine. These will usually involve anaphylactoid/anaphylactic reactions of varying severity (see also

sections 4.3 and 4.4, notably for hypersensitivity to galactose-α-1,3-galactose (alpha-Gal) and allergy to red meat and offal).

Tabulated list of adverse reactions

Immune system disorders

Rare: Anaphylactic/anaphylactoid reactions up to shock (see section 4.4)

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 (ee section 4.4).

Information on particular undesirable effects

Mild anaphylactoid reactions include:
Generalised erythema, urticaria, periorbital oedema, or angiooedema.

Moderate anaphylactoid reactions include:
Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain.

Severe anaphylactoid reactions include:
Cyanosis or $SaO2 \leq 92\%$ at any stage, hypotension (systolic blood pressure < 90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence.

In the event of an anaphylactoid reaction, the infusion must be discontinued immediately and the usual acute treatment given.

Paediatric population

There are no data relating to a special pattern or incidence of adverse reactions in paediatric patients.

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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

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

Mechanism of action

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 causes 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 and 100 % of the infused volume with a volume effect over 4-5 hours.

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 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 effects

Gelofusine substitutes intra- and extravascular volume deficits caused by losses of blood or 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 dieresis are increased without dehydrating the extravascular space.

Paediatric population

Only few clinical studies are available in the paediatric population. In 222 children with dengue shock syndrome aged 1-15 years, Gelofusine, dextran 70, Ringer's lactate, and isotonic saline performed equally well with regard to initial pulse pressure recovery time, subsequent episodes of shock, and development of any complication. Out of 56 children who received Gelofusine, 5 (9%) had an allergic reaction but recovered without sequelae (**Ngo et al 2001**).
In 14 children (mean age 10 months) undergoing surgery who received 15 ml/kg b.w. of Gelofusine during the first hour of surgery to maintain normovolaemia (**Haas et al, 2007**), and in 25 children aged 0-12 years receiving Gelofusine for volume replacement after surgery (10 ml/kg b.w.) median coagulation values remained within the normal range (**Osthaus et al, 2009**). No adverse events occurred in these studies.
In 776 preterm infants administered fresh frozen plasma, Gelofusine, or glucose at a dose of 20 ml/kg b.w. after birth and further 10 ml/kg b.w. after 24 h, no evidence was seen for any adverse short-term outcome related to gelatine use. The developmental outcome after two years was similar in the three groups (**Northern Neonatal Nursing Initiative Trial Group 1996a, 1996b, and Bailey et al 2010).**
In 100 cyanotic paediatric patients (age 6 months to 3 years) undergoing cardiac surgery with cardiopulmonary bypass, Gelofusine 10-20 ml/kg (n = 50) in the priming solution was safe and effective. No adverse events were reported **(Miao et al 2014)**.
Overall, the data available for Gelofusine are too limited to fully assess the efficacy and safety in the paediatric population.(see section 4.2 and 4.4).

5.2 Pharmacokinetic properties

Distribution:

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

Biotransformation/elimination:

The elimination of the modified gelatine takes place in 2 phases, with a half-life of approximately 8 hours for the first phase and a half-life of several days for the second phase. 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 also excreted via kidneys.

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

No additional concerns identified.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections, NaOH for pH adjustment.

6.2. Incompatibilities

There are no known major incompatibilities. Gelofusine Ecobag does not interfere with blood grouping or cross-matching.

6.1. Shelf -Life

Shelf life of the medicinal product as packaged for sale

The shelf-life of Gelofusine Ecobag is 20 months for the 100 ml and 24 months for 250 ml, 500 ml and 1000 ml packs.

Shelf life after first opening the container

Not applicable. Infusion should commence immediately after connecting the container to the giving set.

6.4. Special Precautions for Storage

Dot not store above 25°C
Do not freeze.

6.5. Nature and Contents of Container

Gelofusine Ecobag is available in 100 ml, 250 ml, 500 ml and 1000 ml non PVC.

6.6 Special precautions for disposal

The container overwrap is not sterile. If it is damaged, or fluid is present in the space between the wrap and the container, the container should be assumed to be damaged and should therefore be discarded. The entry port area should be disinfected prior to insertion of the giving set.

Only clear solution should be used; it contains no preservative and any unused Gelofusine Ecobag should be discarded once the seal has been opened. Do not reconnect partially used containers.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

B Braun Melsungen AG
Carl-Braun-Strasse 1
D-34212 Melsungen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PL 03551/0047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/12/2008

10 DATE OF REVISION OF THE TEXT

20/01/2021