SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gelofusine, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml Gelofusine contains:	
Succinylated gelatin (=modified fluid gelatin) (Molecular weight, weight average: 26 500 Dalton)	40.0 g
Sodium chloride	7.0 g
Electrolyte content:	
Sodium	154 mmol
Chloride	120 mmol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
A clear, colourless or slightly yellow aqueous solution.

Physico-chemical characteristics:	
pH	7.4 ± 0.3
Osmolarity	274 mOsm/l

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Colloidal plasma volume substitute for:

- Prophylaxis and treatment of imminent or manifest relative or absolute hypovolaemia and shock
- Procedures involving extracorporeal circulation (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 adminis-

tered is initially 500 to 1000 ml on average, in case of severe blood loss higher doses have to 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.

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.).

Maximum dose

The maximum daily dose is determined by the degree of haemodilution. Care must be taken to avoid a decrease of the haematocrit below critical values see section 4.4.
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

The rate of infusion can be increased by using a pressure cuff around the non-PVC infusion bag or by using an infusion pump. Rapid administration of infusion fluids from a glass bottle or a plastic (polyethylene) container should be avoided in view of the risk of an air embolism.
In general, the infusion of 500 ml should take at least 1 hour.
In severe, acute situations, 500 ml can be administered in 5-10 minutes, until signs of hypovolaemia are relieved.

Special populations

Gelofusine has to be administered with caution to elderly patients and patients with renal impairment (see also section 4.4).

Method of administration

Intravenous use.
When given rapidly Gelofusine should be warmed to not more than 37°C if possible.
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypervolaemia
- Hyperhydration
- Acute congestive heart failure

4.4 Special Warnings and Precautions for Use

Special warnings

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, the first 20 – 30 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**.
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 due to circulatory overload e.g. patients with hypertension, pulmonary oedema or renal insufficiency with oligo- or anuria.
- with severely impaired renal function (see section 5.2)
- having oedema with water/salt retention
- with major blood coagulation disorders
- of advanced age (elderly patients) as those are more prone to develop renal impairement or suffer from other deficiencies than younger patients

Precautions for use

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

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.

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 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.

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 possible anaphylactoid reactions, with consecutive foetal and neonatal distress due to maternal hypotension, the use of Gelofusine should be avoided during pregnancy, unless the clinical condition of the woman requires treatment with the medicinal product.

Breast-feeding
There are no 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 the food. No significant increase in the content of these electrolytes in mother's milk is expected following the use of Gelofusine. Breast-feeding can be maintained following treatment with 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

Not relevant.

4.8 Undesirable Effects

Definition of frequency terms:
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: frequency 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 anaphylactoid/anaphylactic reactions of varying severity. (See 4.4. Special warnings and precautions for use)

Immune system disorders
Rare: Anaphylactoid reactions (all grade) (See 4.4. Special warnings and precautions for use)
Very rare: Severe anaphylactoid reactions (See 4.4. Special warnings and precautions for use)

Cardiac disorders
Very rare: Tachycardia

Vascular disorders
Very rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Very rare: Respiratory difficulties
.Skin and subcutaneous tissue disorders
Rare: Allergic skin reactions

General disorders and administration site conditions
Uncommon: Mild transient increase of body temperature.
Very rare: Fever, chills

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 $SaO_2 \leq 92\%$ 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.

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 national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms

Overdose of Gelofusine may cause hypervolaemia and circulatory overload, with a significant fall in haematocrit and plasma proteins. 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 of circulatory overload, the infusion must be stopped and a rapid-acting diuretic should be given. If an overdose occurs, the patient should be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic 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°500Dalton (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.

The measured initial volume effect of Gelofusine is about 100% of the infused volume with a sufficient volume effect over 4-5 hours.

Gelofusine does not interfere with the determination of blood groups and it is neutral regarding clotting mechanisms.

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 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, 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 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:
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 first are degraded proteolytically in the liver and then 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

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),
Hydrochloric acid (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

Bottle of low dentity polyethylene, 'Ecoflac plus': 3 years
Plastic bags, 'Ecobag' (non-PVC) : 2 years.

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

6.4 Special Precautions for Storage

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

6.5 Nature and Contents of Container

Gelofusine is available in the following containers and pack sizes:

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

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

7. MARKETING AUTHORISATION HOLDER

B.Braun Melsungen AG
Carl-Braun-Straße 1
34212 Melsungen, Germany

Postal address:
B.Braun Melsungen AG
34209 Melsungen, Germany

Tel +49 5661 71 0
Fax: +49 5661 71 4567

8. MARKETING AUTHORISATION NUMBER(S)

To be completed.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

To be completed

10. DATE OF REVISION OF THE TEXT

September 2013