SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gelofusine 40 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml solution contain:

Gelatine polysuccinate (= modified fluid gelatine) (Molecular weight, weight average: 30 000 Dalton Molecular weight, number average: 23 200 Dalton)	40.0	g
Sodium chloride	7.01	g

Electrolyte concentrations

Sodium	154	mmol/l
Chloride	120	mmol/l

Excipients:

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

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

Physicochemical characteristics

pH		7.4 ± 0.3
Relative viscosity (37 °C)		1.9
Isoelectric point	pH	4.5 ± 0.3
Colloid osmotic pressure		453 mm H_2O = 33.3 mm Hg
Theoretical osmolarity		274 mosm/l
Gelation point		≤ 3 °C

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Colloidal plasma volume substitute for

- Prophylaxis and treatment of relative or absolute hypovolaemia and of shock;
- Prophylaxis of hypotension (e.g. during induction of epidural or spinal anaesthesia);
- Procedures involving extracorporeal circulation (e.g. heart-lung machine);
- Acute normovolaemic haemodilution.

4.2 Posology and Method of Administration

Recommended dosage schedule

Adults

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 effect of volume substitution is controlled by monitoring blood pressure, central venous pressure, heart rate, diuresis rate, haemoglobin concentration, haematocrit etc.

Paediatric patients

As documented experience regarding the use of Gelofusine in children is insufficient, the dosage must be adjusted very carefully according to the individual requirements for restoration and maintenance of normal haemodynamic status and circulating fluid volume. See also section **4.4**.

Maximum dose:

From the toxicological point of view there are no limitations of the 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.

Values regarded to be critical for the patient vary interindividually, depending, *inter alia*, on capillary oxygen extraction, the patient's age, circulatory reserve and prevailing clinical condition. In patients with normal oxygen requirement and unimpaired compensatory mechanisms, haemodilution down to a haemoglobin level of 8 g/100 ml or a haematocrit of 25 % may be acceptable; in patients in intensive care the haemoglobin must not fall below 10 g/100 ml or the haematocrit not below 30 %. 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 infusion rate depends on the actual haemodynamic situation. Usually, 500 ml are infused over 30 min. However, the first 20 – 30 ml of solution should be infused slowly in order to detect the occurrence of an anaphylactoid reaction as early as possible. See also sections **4.4** and **4.8**.

In shock situations, up to 20 ml of Gelofusine may be infused per kg body weight (BW) per hour (corresponding to 0.33 ml/kg BW/min). In vital emergencies, Gelofusine may be infused rapidly by pressure infusion, 500 ml within 5 – 10 min.

Too rapid infusion may lead to circulatory overload.

Method of administration

Intravenous use

The solution should be warmed to body temperature prior to infusion.

When giving Gelofusine by pressure infusion (e.g. by pressure cuff or infusion pump), all air must be removed from containers with air space inside and from the infusion set before the solution is administered.

4.3 Contraindications

Gelofusine must not be administered in case of:
- hypersensitivity to any of the constituents of the solution,
- hypervolaemia,

– hyperhydration,
– severe cardiac insufficiency,
– severe blood coagulation disorders.

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.

Gelatin preparations for volume replacement may rarely cause anaphylactoid reactions of varying degrees of severity. In order to detect the occurrence of an anaphylactoid reaction as early as possible, the first 20 – 30 ml should be infused slowly and under careful observation of the patient. Details of symptoms of anaphylactoid reactions and emergency measures, see section **4.8, Undesirable effects**.

Gelofusine should only be administered with caution to

- elderly patients
- patients at risk due to circulatory overload e.g. patients with congestive heart failure, right or left ventricular insufficiency, hypertension, pulmonary oedema or renal insufficiency with oligo- or anuria.

In such cases Gelofusine should only be given under careful monitoring of the patient's hamodynamic situation.

There is no sufficient experience with the use of Gelofusine in children. Therefore, Gelofusine should be used in children only after careful benefit-risk assessment, and with careful monitoring.

Precautions for use

Checks of serum electrolyte concentrations and water balance are necessary, in particular in patients with hypernatraemia, hypokalaemia, dehydration, 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.

In states of dehydration the fluid deficit must be corrected first. Electrolytes should be substituted as required.

During compensation of severe blood losses by infusions of large amounts of Gelofusine, the haematocrit must be monitored under any circumstances. The haematocrit should not decrease below the critical values stated in section **4.2**.

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".

Interference with laboratory tests

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

Pharmacological interactions are not known.

4.6 Pregnancy and Lactation

Controlled studies have been carried out neither in animals nor in pregnant women.

Because of possible anaphylactoid reactions, the medicinal product should only be administered during pregnancy, if the indication is imperative, and solely if the potential benefit is greater than the foetal risk.

It is not known whether Gelofusine passes into breast milk. Sufficient experience with application during the breast-feeding period is not available.

4.7 Effects on Ability to Drive and Use Machines

None known

4.8 Undesirable Effects

The only potentially serious adverse reactions are the anaphylactoid reaction described below. However, severe reactions are very rare.

Immune system disorders

Rare (≥ 1/10,000 to < 1/1,000):
Anaphylactoid reactions (all grades). (Details see section "Anaphylactoid reactions" below)

Very rare (< 1/10,000):
Severe anaphylactoid reactions (grade III or IV) (Details see section "Anaphylactoid reactions" below)

Gastrointestinal disorders

Uncommon (≥ 1/1,000 to < 1/100):
Transient mild nausea or abdominal pain

General disorders

Uncommon (≥ 1/1,000 to < 1/100):
Transient mild rise of body temperature

Anaphylactoid reactions

After the administration of Gelofusine infusions, just as of any colloidal volume substitutes, anaphylactoid reactions of varying degrees of severity may occur. These reactions manifest as fever, cutaneous eruptions (urticaria), sudden flushing of face and neck and a drop of blood pressure. In very rare cases they may proceed to shock, cardiac and respiratory arrest.

Severe anaphylactoid reactions (grade III or IV) are very rare (incidence < 1 : 10 000). Patients receiving Gelofusine must be continuously observed for the occurrence of anaphylactoid reactions.

General guidelines for the prophylaxis of adverse reactions:

- Adequate information of physicians and nursing staff about the type and severity of possible adverse reactions that may be encountered after the administration of a colloidal volume substitute.
- Careful observation of the patient during infusion, especially while the first 20 – 30 ml of the solution are being infused.

- Immediate availability of all equipment and medication for cardio-pulmonary resuscitation.
- Stop of infusion immediately, as soon as there are any signs of adverse reactions.

Emergency treatment of anaphylactoid reactions follows established schedules, depending on the severity of the reaction[1].

It cannot be predicted by any test procedure which patients are likely to experience anaphylactoid reactions, nor is it possible to foresee the course and severity of any such reaction.

Anaphylactoid reactions caused by gelatin solutions may either be histamine mediated or histamine independent. Histamine release can be prevented by the use of a combination of H_1- and H_2 receptor blockers. Prophylactic administration of corticosteroids has not proven effective.

Prophylactic administration of corticosteroids has not proven effective.

Adverse reactions may occur in conscious and anaesthetized patients. In the acute phase of volume deficiency shocks so far no anaphylactoid reaction has ever been reported.

4.9 Overdose

Overdose or too rapid infusion of Gelofusine would lead to unintended hypervolaemia and circulatory overload, associated with consecutive impairment of heart and lung function. Symptoms of circulatory overload are e.g. headache, dyspnoea, and jugular vein congestion.

As soon as symptoms of circulatory overload appear, the infusion must be stopped immediately. Therapy is symptomatic. Administration of a diuretic may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Gelofusine is a 4 % w/v solution of succinylated gelatine (also known as modified fluid gelatine) with an average molecular weight of 30 000 Dalton (weight average). It has a relative viscosity of 1.9 at 37 °C and a colloid-osmotic pressure of 34 mmHg. The iso-electric point is at pH 4.5 The negative charges introduced into the molecule by succinylation lead to an expansion of the molecule, thus rendering it markedly more voluminous than unsuccinylated protein chains of the same molecular weight.

The characteristics of Gelofusine result in a sufficient volume effect over about 3 – 4 hours

Therapeutic effect:

Gelofusine substitutes intravascular volume deficits caused by losses of blood or plasma. Thus the mean arterial pressure, the left-ventricular end-diastolic pressure, the cardiac stroke volume, the cardiac index, the oxygen supply and the diuresis are increased.

Mechanism of action:

The colloid-osmotic pressure of the solution determines the extent of its initial effect. The duration of the effect depends on the clearance of the colloid by re-distribution and excretion. The volume effect of Gelofusine is equivalent to the administered amount of solution. So Gelofusine is a plasma substitute, it does not have a plasma expanding effect. Lost plasma protein is not substituted by Gelofusine.

[1] e.g. Adams HA et al.: Empfehlungen zur Diagnostik und Therapie der Schockformen der IAG Schock der DIVI, Teil 4: Anaphylaktischer Schock
Intensivmed.42 (2005): 299 – 304

5.2 Pharmacokinetic Properties

Distribution:
After infusion, Gelofusine is rapidly distributed in the intravascular compartment. There is no evidence that Gelofusine is stored in the reticulo-endothelial system or elsewhere in the organism.

Metabolism/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 first are degraded proteolytically in the liver and then are also excreted renally. The proteolytic metabolism is so adaptable that even under the condition of renal insufficiency no accumulation of gelatine is observed.

Pharmacokinetics in special clinical situations:
The plasma half-life time of Gelofusine may be prolonged in patients on haemodialysis (GFR < 0.5 ml/min).

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity and toxicity to reproduction.

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,
Water for injections

6.2 Incompatibilities

Account should be taken of incompatibilities that may occur in combination with other drugs. Gelofusine should generally not be mixed with other infusion solutions.

Before adding drugs or other additives to Gelofusine, information on compatibility should be obtained from the manufacturer.

6.3 Shelf Life

Shelf life of the medicinal product as packaged for sale

Polyethylene containers: 3 years

Plastic bags “Ecobag” (non-PVC):

100 ml:	20 months
250 ml, 500 ml, 1000 ml	24 months

Shelf life after first opening the container

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

Shelf life after dilution or reconstitution according to directions

Not applicable.

6.4 Special Precautions for Storage

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

6.5 Nature and Contents of Container

Gelofusine is supplied in

– Containers of low-density polyethylene, contents: 500 ml
– Plastic bags “Ecobag” (non-PVC), contents: 100 ml, 250 ml, 500 ml, 1000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product is supplied in single-dose containers. Unused contents of an opened container must be discarded.

Only to be used if solution is clear and free of precipitate and the container undamaged.

Use immediately after connecting container to the giving set.

After admixture of an additive start administration immediately.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

...

10 DATE OF REVISION OF THE TEXT

04-2010