Gelofusine®

Modified Fluid Gelatin

Tried and Tested worldwide

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SHARING EXPERTISE

Modified Fluid Gelatin

Tried and Tested worldwide

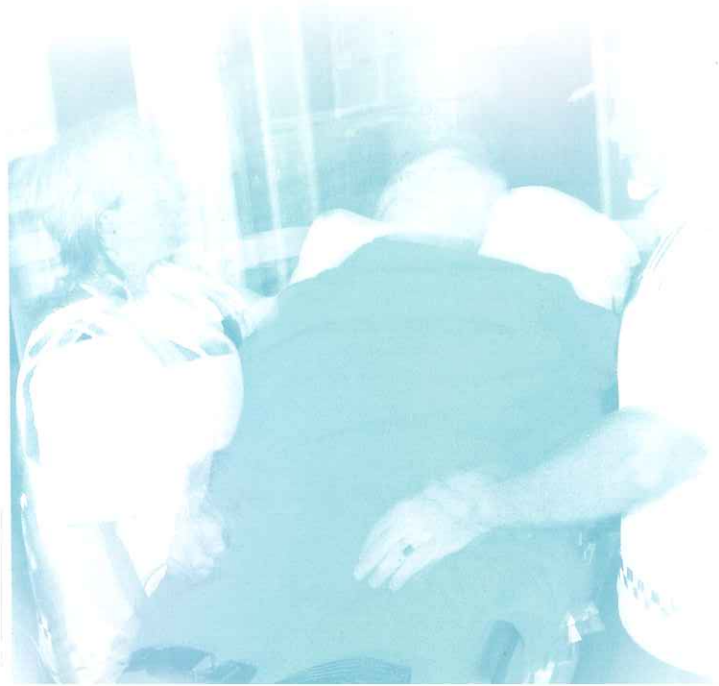
Gelofusine® is a colloidal volume replacement fluid based on 4% modified fluid gelatin.

Several decades of experience in production and use of modified fluid gelatins recommend B. Braun as an excellent partner in the field of volume replacement solutions.

In comparison with other synthetic colloids Gelofusine® offers a number of important advantages:

User benefits

- Wide range of therapeutic indications
- Readily controllable volume effect over 3-4 hours
- No effect on blood coagulation
- Compatible with blood and blood products
- No dose limit



Clinical

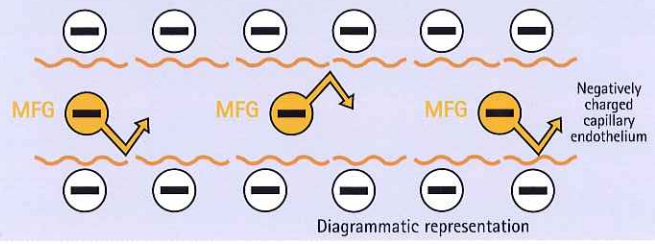
Plasma Volume Replacement

Mechanism of Action

Molecular Negative Charge

One factor that affects the performance of a colloid is its negative charge. The capillary endothelium is negatively charged and the greater the charge on the molecule, the greater the repelling force.

The colloid molecules in Gelofusine® have a significant negative charge.

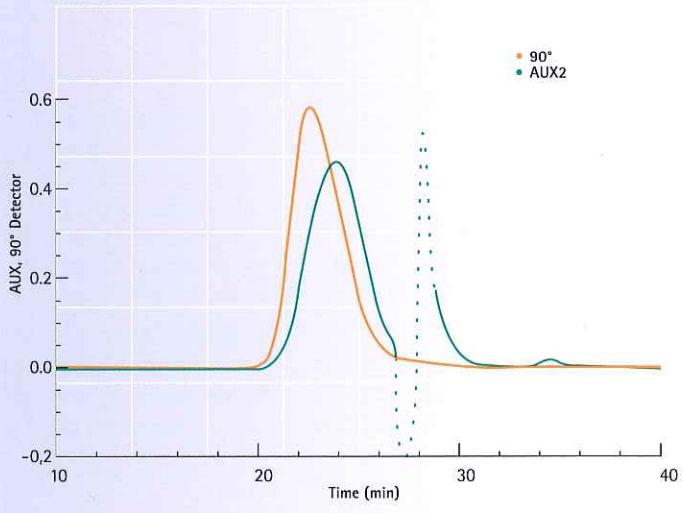


Diagrammatic representation

Molecular Weight Spread

Molecular spread of a colloid will influence its volume effect and duration of action. Colloids with a wide molecular spread are less well retained within the intravascular compartment. Gelofusine® has a narrow molecular weight profile as indicated by the graph opposite and by its poly-dispersity ratio of 1.28.

Spread of colloid molecules within Gelofusine® using Gel Permeation Chromatography (GPC).

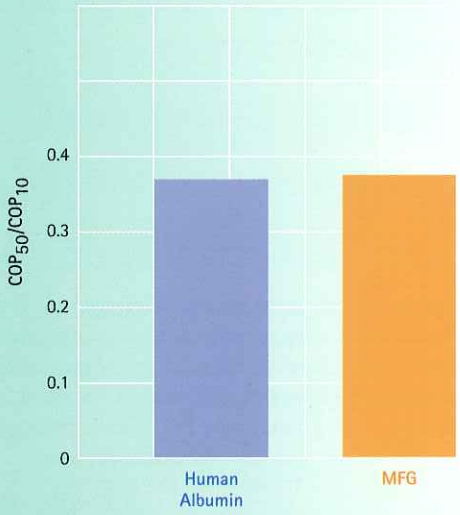


Detector 1. – Multi-Angle Laser Light Scattering (MALLS)
Detector 2. – Refractive Index

COP_{50}/COP_{10} Ratio

COP_{50}/COP_{10} ratio is an indicator of a colloid's retention in the circulation. A difference in this ratio could indicate differences in retention.

Gelofusine® has a COP_{50}/COP_{10} ratio which indicates its retention is likely to be comparable with Albumin.



Adapted from Webb A. R. Int Care Med 1989 [1]

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Clinical

Mechanism of Action

Adequate volume replacement for hypovolaemic patients is only possible if a sufficiently high oncotic pressure can be maintained so that sufficient fluid is retained intravascularly.

Following blood or plasma loss Gelofusine®:

- Maintains colloid osmotic pressure
- Maintains adequate filling of intravascular compartment

Colloidal plasma substitutes can be categorised as follows

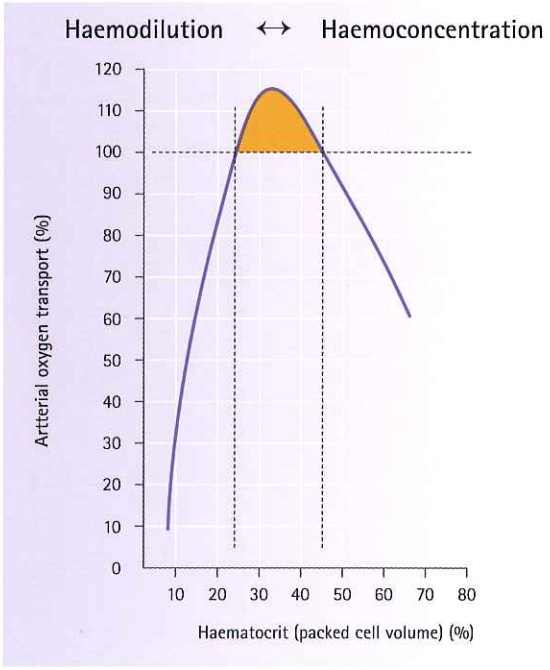
Hypo-oncotic solutions	oncotic pressure less than plasma	infused volume > effective volume
Iso-oncotic solutions	oncotic pressure approximately equal to plasma	infused volume = effective volume
Hyper-oncotic solutions	oncotic pressure greater than plasma	infused volume < effective volume

Gelofusine® is iso-oncotic. The initial increase in plasma volume after infusion corresponds approximately to the volume infused. The volume effect lasts approximately 3-4 hours [2]. Iso-oncotic solutions are preferred over hyper-on-cotic solutions for treatment of moderate hypovolaemia and for peri-operative volume replacement, since there is no danger of dehydration of the extracellular space.

The effects of Gelofusine® are primarily achieved by two mechanisms:

- Increase in plasma volume
- Haemodilution

Both effects lead to an increase of cardiac output as a result of the increased venous return. The arterial oxygen transport is maintained in spite of reduced oxygen transport capacity. The greater the volume deficiency is, and the more rapidly the infusion is carried out, the more marked are the changes in haemodynamics and oxygen transport [3].



Clinical

Distribution

After intravenous infusion, Gelofusine® is rapidly distributed in the intravascular compartment. Acute hypovolaemia before administration of Gelofusine® does not influence distribution or elimination [5].

Metabolism and Elimination

Investigations do not indicate important metabolism of Gelofusine® [6]. Approximately 1 to 3% of the Gelofusine® infused is metabolised by endogenous peptidases [6] and is eliminated mainly via the kidneys by glomerular filtration [7]. There is no evidence of prolonged retention in any organ [5].

The elimination of Gelofusine® occurs very rapid. Mishler [8] reported from early investigations that 24 hours after administration of Modified Fluid Gelatin, 12% was to be found in plasma, 62% in urine and 26 % in the extravascular space.

The vast majority of the Gelofusine® administered is eliminated in the urine and only a small amount of the dose is excreted in the faeces [6].

Side Effects

Effects on haemostasis and coagulation

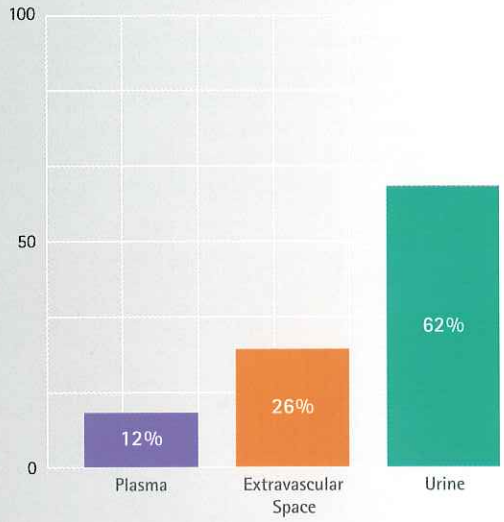
Experimental and clinical investigations have not revealed any clinically relevant specific influence of Gelofusine® on blood coagulation. There is no dosage limit for Gelofusine®. However, dilution of the haematocrit should be taken into account by the clinician [9].

Anaphylactoid/anaphylactic reactions

Gelofusine® may, as occurs with every other substance employed therapeutically, elicit hypersensitivity reactions. An investigation of 1585 patients who exhibited an anaphylactic reaction during the peri-operative period revealed that less than 5% were caused by colloidal volume replacement solutions. The majority of these were limited to skin and mucous membranes (grade I and II) [10, 10a].

The mechanisms that lead to these reactions can be considered both allergic (anaphylactic) and non-allergic (anaphylactoid). The anaphylactoid reactions are most probably caused by a non specific release of histamine from mast cells [11].

Distribution and elimination of modified fluid gelatin (Gelofusine®) at 24 hours after administration



Adapted from Mishler Clin. Heamatol. 1984 [8]

Pyrogen testing is of great importance to ensure anaphalactoid reactions are kept to a minimum. Gelofusine® is tested to a higher level of safety than is currently required by the EU to ensure that the chances of an adverse reaction are minimal [12].

Toxicology

The colloid in Gelofusine® has been available as a plasma volume substitute for more than 30 years. A vast body of evidence exists on it. In respect of local tolerance and other specific toxicological investigations Gelofusine® does not show detrimental pharmacological effects on the blood clotting system or local effects after subcutaneous administration.

Gelofusine® displays neither antigenic nor convulsant effects. These results are in agreement with clinical experience. Anaphylactic reactions have been reported and are the only serious clinically relevant side-effects.

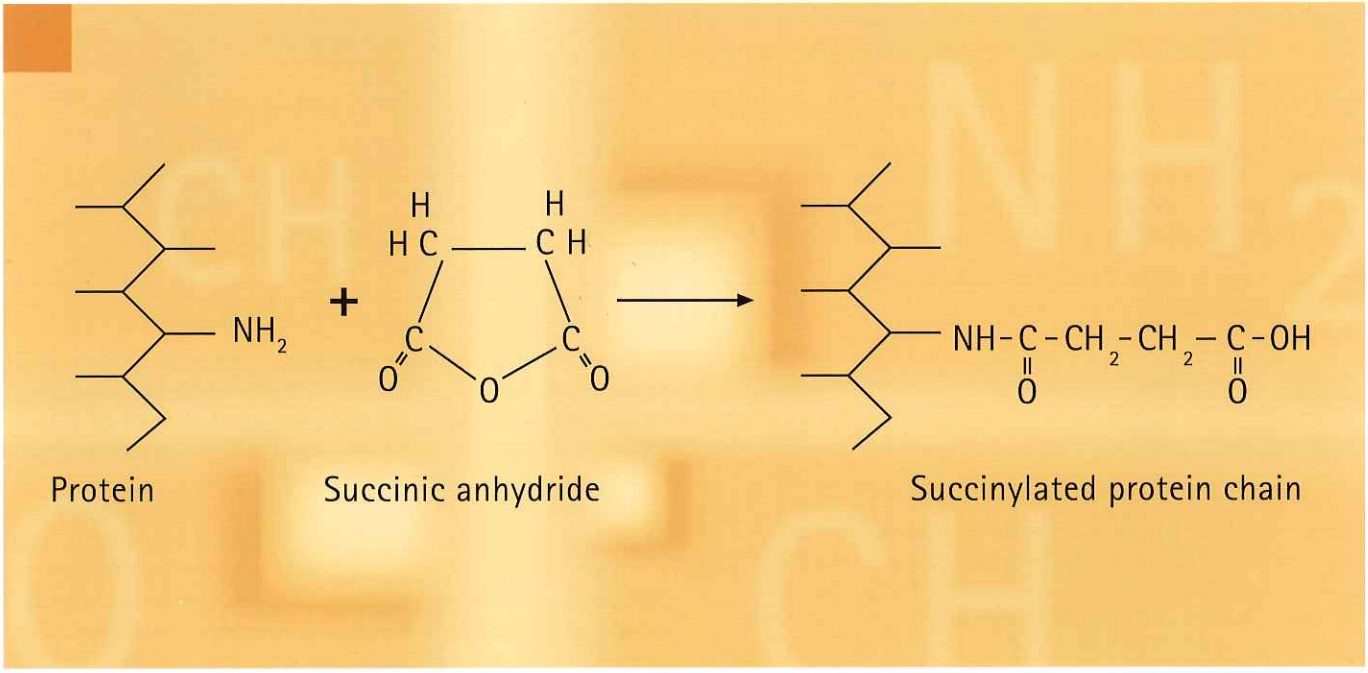
During pregnancy Gelofusine® should only be administered after strict consideration of the risks and benefits. Although no evidence is available that Gelofusine® is embryotoxic, the risk of anaphylactic/anaphylactoid reactions can not be totally excluded.

No experience is available concerning the administration during lactation or the administration to children up to one year of age.

Non-Clinical

Manufacture/ Production Process

After thermal degradation of the purified animal collagen to protein strands and removal of the inactive, low molecular weight fractions that would migrate through the capillary wall, the material is reacted with succinic anhydride (succinylation) and adjusted to a weight average molecular weight of 30000 Dalton. During this process the basic NH2- groups of the protein molecules react with the succinic anhydride to yield carboxyl groups according to the following scheme:



The succinylation of the protein chain confers a charged structure on it that leads to an expansion of the molecule so that it occupies considerably more space than a non succinylated protein chain of the same molecular weight [13]. The negative charge also means that there is a repelling force acting between the molecule and the capillary (see page 2).

Packaging

Over the course of many years, much effort has been applied to develop non-PVC materials offering the benefits and omitting the disadvantages of plasticised PVC.

B. Braun has introduced the Ecobag to reduce safety concerns.

Ecobag is manufactured by the co-extrusion of three different polymer foils:

- Outer Layer - Polyester
- Core Layer - Polyethylene
- Inner Layer - Polypropylene

User benefits Ecobag

- Container collapses fully
- Container suitable for pressure infusion devices
- Re-sealable ports
- Long shelf life
- No leaching of plasticisers into solution
- Improved ecological profile

The disadvantages of PVC include:

- Presence of plasticisers
- Limited compatibility with lipophilic preparations and certain drugs
- Poor ecological profile

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Gelofusine®

Plasma Volume Replacement

Gelofusine®

Composition
1000 ml infusion solution contains:

Active ingredients

Succinylated gelatin (Modified fluid gelatin)	40.00 g
Weight average molecular weight (Mw) 30 000	
Number average molecular weight (Mw) 23 200	
Sodium chloride	7.01 g
Sodium hydroxide	1.36 g

Excipients
Water for injections

Electrolyte concentrations

Sodium	154 mmol/l
Chloride	120 mmol/l

Physico-chemical characteristics

Theoretical osmolarity	274 mOsm/l
pH	7.1–7.7
Gel point	≤ 3 °C

Pharmaceutical Form
Solution for infusion.

Pharmaco-therapeutic Group
Colloidal plasma volume substitute.

Therapeutic Indications
As a colloidal volume substitute for
- prophylaxis and treatment of absolute and relative hypovolaemia (e.g. following shock due to haemorrhage or trauma, perioperative blood losses, burns, sepsis)
- prophylaxis of hypotension (e.g. in connection with induction of epidural or spinal anaesthesia)
- haemodilution
- extra-corporeal circulation (heart-lung machine, haemodialysis)
- increasing the leukocyte yield in leucapheresis

Contra-indications
Gelofusine® must not be administered in cases of
- known hypersensitivity to gelatin
- hypervolaemia
- hyperhydration
- severe cardiac insufficiency
- severe disturbance of blood coagulation

Gelofusine® may only be administered with great caution in cases of
- hypernatraemia, since additional sodium is administered with Gelofusine®;
- states of dehydration, since in such cases it is primarily the fluid balance that requires correction;
- disturbance of blood coagulation, since administration leads to dilution of coagulation factors;
- renal insufficiency, since the normal excretion route may be impaired;
- chronic liver disease, since here the synthesis of albumin and coagulation factors can be afffected and administration brings about a further dilution.

Precautions for Use
The following precautions must be taken into account:
Electrolytes should be substituted as required.
Necessary monitoring:
It is necessary to monitor the serum ionogram and fluid balance. This is particularly the case in hypernatraemia, states of dehydration and renal insufficiency.
In cases of blood coagulation disturbances and chronic liver disease the coagulation parameters and serum albumin should be monitored. Because of the possibility of allergic (anaphylactic/anaphylactoid) reactions, appropriate monitoring of patients is necessary.

Special Warnings
Paediatric Use
No experience is available concerning administration in children less than one year of age.

Use in Pregnancy and Lactation
There is no evidence of an embryotoxic effect of Gelofusine®. However, because the possibility of an allergic (anaphylactic/anaphylactoid) reaction cannot be excluded, administration should only be carried out during pregnancy after critical evaluation of the risks and benefits. No information is available concerning the passage of Gelofusine® into mother's milk.

Undesirable Effects
As with all colloidal volume substitutes, allergic (anaphylactic/anaphlactoid) reactions of varying severity can occur after infusion of Gelofusine®. These reactions manifest themselves as skin reactions (urticaria) or can result in a flushing of the face and neck. In rare cases, a drop in blood pressure, shock or cardiac and respiatory arrest could occur.

The information contained in this excerpt of the Standard Product Information may differ with regard to national approved indications, contraindications etc.

For further information please contact our local B. Braun representative or write to

B. Braun Australia Pty Ltd
17 Lexington Drive, Bella Vista NSW 2153

References

1. Webb A. R. Int Care Med. 1989: 15: p 116-120
2. Lutz H. Deutsche Apotheker Zeitung 123, 51: 253-258 (1983)
3. Lutz H. Georg Thieme Verlag Stuttgart: 38-73 (1975)
4. Lutz H.: Georg Thieme Verlag Stuttgart: 128 - 130 (1986)
5. Zekorn D. In: Lundsgaard-Hansen P. Bibl. Haema No. 33. 131-140 (1969)
6. Hartig W. Moderne Infusionstherapie: 6.4 561-572 (1993)
7. Lundsgaard-Hansen P. Prog. Clin. Biol. Res. 19: 227-257 (1978)
8. Mishler J. M. Clin. Haemat. 13/1: 75-92 (1984)
9. SPC and Prescribing Information
10. Laxenaire M. Ann. Fr. Anesth. Reanim. 13: 301-310 (1994)

10a. Laxenaire M. Ann. Fr. Anesth. Reanim. 12: 91-96 (1993)

11. Lorenz W. The Lancet 343: 933-940 (1994)
12. Data on file
13. Himpe D. Journal of Card Vasc Anes. 5, 5:457-466 (1991)

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