Public Assessment Report

Decentralised Procedure

Gelaspan solution for infusion

(Succinylated gelatin, sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate)

Procedure No: UK/H/3634/001/DC

UK Licence No: PL 03551/0120

B. Braun Melsungen AG
LAY SUMMARY
Gelaspan solution for infusion
(Succinylated gelatin, sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate)

This is a summary of the public assessment report (PAR) for Gelaspan solution for infusion (PL 03551/0120; UK/H/3634/001/DC). It explains how the application for Gelaspan solution for infusion was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Gelaspan solution for infusion.

For practical information about using Gelaspan solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Gelaspan solution for infusion and what is it used for?
Gelaspan solution for infusion is a medicine with a ‘well-established use’. This means that the medicinal use of the active substances of this product has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Gelaspan solution for infusion is used to replace blood and body fluid, which have been lost as a result of, for example, an operation, an accident or a burn.

How does Gelaspan solution for infusion work?
Gelaspan solution for infusion contains the active ingredients, succinylated gelatin, sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate. This medicine is a plasma volume substitute and it replaces fluid lost from the circulation.

How is Gelaspan solution for infusion used?
This medicine can only be obtained with a prescription.

Gelaspan solution for infusion will be given intravenously (into a vein), i.e. by a drip.

In adults the amount of medicine given and duration will depend on how much blood or fluid has been lost and on the patient’s condition.

There is only little experience of the use of Gelaspan in children. A doctor will only administer this medicine to a child if he/she considers it essential for a child’s recovery. In those cases the clinical condition of a child will be taken into account and his/her therapy will be monitored especially carefully. The doctor will carry out tests (on blood and blood pressure, for example) during treatment, and the dose of Gelaspan will be adjusted according to the patient’s need.

In case of pressure infusion, all air must be removed from the container and the infusion set before the solution is administered.

What benefits of Gelaspan solution for infusion have been shown in studies?
As succinylated gelatin, sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate are well-known substances and their use in the licensed indication is well established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the active substances for use in the licensed indication.

What are the possible side effects of Gelaspan solution for infusion?
Like all medicines, this medicine can cause side effects, although not everybody gets them.
For the full list of side effects reported with Gelaspan solution for infusion, see section 4 of the package leaflet, available on the MHRA website.

For the full list of restrictions, see the package leaflet.

**Why was Gelaspan solution for infusion approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Gelaspan solution for infusion outweigh the identified risks and recommended that the product be approved for use.

**What measures are being taken to ensure the safe and effective use of Gelaspan solution for infusion?**
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

**Other information about Gelaspan solution for infusion**
Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain, Sweden, the Netherlands and the UK agreed to grant a Marketing Authorisation for Gelaspan solution for infusion (PL 03551/0120) on 18 May 2011. A Marketing Authorisation was granted in the UK on 14 June 2011.

The full PAR for Gelaspan solution for infusion follows this summary.

This summary was last updated in July 2017.
# SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Gelaspan solution for infusion (PL 03551/0120; UK/H/3634/001/DC), is approvable. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain, Sweden and the Netherlands as Concerned Member States (CMS).

This product is a prescription only medicine (legal classification POM).

Gelaspan is a colloidal plasma volume substitute in an isotonic, fully balanced electrolyte solution for prophylaxis and treatment of imminent or manifest relative or absolute hypovolaemia and shock.

This application was made under the Decentralised Procedure (DCP), according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

This product contains the active substances succinylated gelatin, sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate.

The colloid-osmotic pressure of the solution determines 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 Gelaspan is equivalent to the administered amount of solution, Gelaspan 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. Gelaspan is isotonic, it therefore does not cause fluid shifts into the intracellular space as caused by hypotonic solutions.

Gelaspan contributes in the restoration of electrolyte balance and the correction of acidosis. Gelaspan is lactate free and can be used in patients with liver diseases. As a precursor of bicarbonate the solution contains acetate which is metabolisable in all organs and muscles.

No new clinical or non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The company has provided a justification for not submitting a risk management plan (RMP) as the product may replace other succinylated gelatin containing products already marketed and there is more than 10 years post-authorisation experience with the active substances. This justification is acceptable.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The member states considered that the application could be approved at the end of procedure on 18 May 2011. After a subsequent national phase, a licence (PL 03551/0120) was granted in the UK on 14 June 2011.
II QUALITY ASPECTS

II.1 Introduction
Gelaskan solution for infusion is a clear, colourless or slightly yellowish solution with an osmolality of 284 mosmol/l and a pH of 7.4 ± 0.3.

The solution contains 40 g succinylated gelatin, 5.55 g sodium chloride, 3.27 g sodium acetate trihydrate, 0.30 g potassium chloride, 0.15 g calcium chloride dihydrate and 0.20 g magnesium chloride hexahydrate as active ingredients. Other ingredients consist of the pharmaceutical excipients, namely sodium hydroxide, hydrochloric acid and water for injections. All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is supplied in:
- Bottles of low-density polyethylene “Ecoflac plus”, containing 500 ml available in packs of 10 × 500 ml
- Plastic bags “Ecobag” (non-polyvinylchloride (PVC)), sealed with halogenbutyl rubber stoppers containing 500 ml available in packs of 20 × 500 ml

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substances

rINN: Succinylated gelatin
Chemical name: Succinylated gelatin
Molecular formula: R – NH – CO – CH₂ – CH₂ - COOH
Molecular weight: 32'500 Da
Appearance: Succinylated gelatin is a clear, yellow and viscous liquid containing 20 % w/v of succinylated gelatin.

Succinylated gelatin is not the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, succinylated gelatin, are described in the dossier and follow in-house specifications.

rINN: Sodium chloride
Chemical name: Sodium chloride
Molecular formula: NaCl
Molecular weight: 58.44 g/mol
Appearance: Sodium chloride is a white, crystalline powder or colourless crystals or white pearls, freely soluble in water and practically insoluble in ethanol.

rINN: Potassium chloride
Chemical name: Potassium chloride
Molecular formula: KCl
Molecular weight: 74.55 g/mol
Appearance: Potassium chloride is a white, crystalline powder or colourless crystals, freely soluble in water and practically insoluble in ethanol.

rINN: Calcium chloride dihydrate
Chemical name: Calcium chloride dihydrate
Molecular formula: CaCl$_2$, 2 H$_2$O
Molecular weight: 147.0 g/mol
Appearance: Calcium chloride dihydrate is a white, crystalline powder, hygroscopic, freely soluble in water, soluble in ethanol.

rINN: Magnesium chloride hexahydrate
Chemical name: Magnesium chloride hexahydrate
Molecular formula: MgCl$_2$, 6 H$_2$O
Molecular weight: 203.3 g/mol
Appearance: Magnesium chloride hexahydrate are colourless crystals, hygroscopic, very soluble in water and freely soluble in alcohol.

rINN: Sodium acetate trihydrate
Chemical name: Sodium acetate trihydrate
Molecular formula: C$_2$H$_3$NaO$_2$, 3 H$_2$O
Molecular weight: 136.1 g/mol
Appearance: Sodium acetate trihydrate are colourless crystals, very soluble in water and soluble in alcohol.

The active substances, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate and sodium acetate trihydrate, are simple inorganic salts.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate an aqueous, sterile solution which mimics the plasma’s electrolyte pattern rather than a product adjusting the osmolarity.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using the minimum commercial scale batch sizes and has shown satisfactory results. The applicant has committed to perform further process validation on three full scale commercial-scale batches.

Finished Product Specification
The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 2 years for unopened polyethylene containers.
“Ecoflac plus” and plastic bags “Ecobag” (non-PVC) with special storage conditions “Do not store above 25°C” and “Do not freeze”.

Once the container is opened the infusion should commence immediately after connecting the container to the giving set.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
Pharmacodynamic, pharmacokinetic and toxicological properties of the preparation containing succinylated gelatin in a balanced electrolyte solution (sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dihydrate and magnesium chloride hexahydrate) are well known. As these are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
An acceptable justification for not performing an environmental risk assessment has been provided.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical data have been submitted and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of the active substances. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
Since the electrolytes and acetate contained in Gelaspan solution for infusion are physiologically occurring substrates in the human body, in general, they follow the physiological pathways of the organism. The applicant stated that the pharmacokinetics of the individual constituents are not negatively affected by the simultaneous administration of all components.
Limited data is available on the pharmacokinetics of gelatin in humans. The applicant has provided a discussion on what is available to characterise the pharmacokinetics of gelatin and the balanced solution it is supplied in. The applicant has in addition stated that the pharmacokinetics of the individual constituents are not negatively affected by the simultaneous administration of all components. This product contains acetate and a reduced concentration of chloride compared to some other gelatin based products currently licensed in the EU but there are similar products which have been approved in the EU. The applicant has stated that the efficacy and safety of these solutions are established and that the physicochemical properties and the intravascular persistence of succinylated gelatin will not be altered by the minor modifications introduced in Gelaspan.

IV.3 Pharmacodynamics

Gelaspan is a 4% solution of fluid gelatin polypeptides extracted from bovine collagen and cross-linked with succinic acid anhydride. The weight averaged molecular weight is 30,000 Daltons but the distribution of size around this mean is not normal and thus the number averaged molecular weight is 23,200 Daltons. The theoretical osmolarity is 284 mOsm/l, which is comparable to the values of normal plasma.

When Gelaspan is infused intravenously (i.v.), it has an immediate plasma volume effect (depending on the condition of the patient) and the resulting haemodilution effect stabilises or improves haemodynamic parameters. Based on the iso-oncotic properties gelatin solutions in general do not have a volume-expanding effect but replenish plasma volume. Thus, the degree of plasma volume effect depends on the volume of solution infused.

Crystalloids such as balanced electrolyte solutions with lactate or acetate play a definite role in rehydration and fluid resuscitation in critically ill patients, including dehydrated patients, trauma patients, patients with sepsis as well as patients undergoing surgery. In the acutely ill patient there is frequently a dissociation between compartment changes and although the interstitial fluid volume may have even doubled, the plasma volume may be diminished as a result of a gradual loss of plasma into inflamed tissue or from the bowel, or as a result of generalised increase capillary permeability.

IV.4 Clinical efficacy

No clinical trials have been performed with Gelaspan solution for infusion. The applicant stated that since the components of this medicinal product have been used for many decades, comprehensive information exists on their biochemistry, pharmacology, toxicology and clinical use. As a result, the applicant has provided evidence of the safety and efficacy of this medicinal product by referring to published literature.

Several studies across a range of therapeutic indications have been summarised by the applicant. The applicant discusses the role of gelatin in the efficacy of the product, the role of the balanced electrolyte solution and the role of the combination as it appears in Gelaspan solution for infusion.

IV.5 Clinical Safety

The applicant has provided a literature safety review of this product and other similar products. No new safety issues have been identified.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
A satisfactory justification has provided a justification for not submitting a risk management plan (RMP).

**IV.7 Discussion of the clinical aspects**

There are no objections to the approval of this application from a clinical point of view.

**V. USER CONSULTATION**

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with the active substances is considered to have demonstrated the therapeutic value of the compounds. The use of gelatin-based products is well established. The applicant has provided a summary on the pharmacology, efficacy and safety of the product. The balanced solution used in Gelaspan contains electrolytes at levels consistent with physiological levels in plasma. The role of acetate in this solution is justified from a clinical perspective and proposes to offer some advantages over those supplied in non-balanced solutions. The benefit-risk assessment is therefore considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling is listed below:
# Gelaspan solution for infusion

1000 ml solution contain:

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylated gelatine</td>
<td>40.0 g</td>
</tr>
<tr>
<td>Molecular weight, weight average: 26 500 Dalton</td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>5.55 g</td>
</tr>
<tr>
<td>Sodium acetate trihydrate</td>
<td>3.27 g</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.30 g</td>
</tr>
<tr>
<td>Calcium chloride dihydrate</td>
<td>0.15 g</td>
</tr>
<tr>
<td>Magnesium chloride hexahydrate</td>
<td>0.20 g</td>
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**Electrolyte concentrations**

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<th>Concentration</th>
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<tr>
<td>Sodium</td>
<td>151 mmol/l</td>
</tr>
<tr>
<td>Chloride</td>
<td>103 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>4 mmol/l</td>
</tr>
<tr>
<td>Calcium</td>
<td>1 mmol/l</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1 mmol/l</td>
</tr>
<tr>
<td>Acetate</td>
<td>24 mmol/l</td>
</tr>
</tbody>
</table>

**For Single use only**

Use only clear solution ensuring it is practically particle free, from intact container.

Use immediately after first opening.

Do not store above 25 °C.

Do not freeze.

Marketing Authorisation number

UK: PL 03553/0120

IE: PA 736/34/1

**POM**

**Solution for infusion.**

Intravenous use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

**Ecobag®**

20 x 500 ml

**BRAUN**

**B. Braun Melsungen AG**

34099 Melsungen

Germany

**UK Distributor:**

B. Braun Medical Ltd.

Thorncliffe Park

Sheffield S55 2PW

**IE Distributor:**

B. Braun Medical Ltd.

3 Nuns Road Industrial Park

Dublin 12

**Batch:**

**EXP:**

FV 32593
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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