

HAEMACCEL

Polygeline infusion solution 3.5% w/v

Composition

1000 mL of Haemacel contains:

Polygeline: 35 g

Cations:

Na+: 145 mmol

K+: 5.1 mmol

Ca⁺⁺: 6.25 mmol

Anions:

Cl⁻: 145 mmol

Traces of PO₄³⁻ and SO₄²⁻; in addition, anionic polypeptides up to the isoionic point.

Water for injections. B.P.

Description

Haemacel is manufactured from gelatin derived from BSE-free bovine material sourced only from Belgium, Canada, Denmark, Finland, France, Greece, Luxemburg, the Netherlands, Spain, Switzerland, Germany, Italy and Austria. Haemacel is sterile and pyrogen free and contains no preservatives. Viscosity measurements have shown that freezing and thawing will not produce any changes in its physico-chemical properties.

Physico-chemical data:

	Haemacel 3.5%	Albumin 5%
Mean Molecular weight (Dalton)	approx. 30 000	66 000
Relative viscosity (35°C)	1.7 - 1.8	1.9 - 2.3
Dynamic viscosity	cP 1.15 - 1.20	1.12
Isoelectric point	pH 4.7 (\pm 0.3)	4.9 (\pm 0.2)
pH of infusion solution	7.3 \pm 0.3	7.2 \pm 0.1
Colloid-osmotic pressure (oncotic) (37°C)	3.4 - 3.8 Kpa	3.2 - 3.4 Kpa
Osmolality	293 mOsm/kg	
Osmolarity	301 mOsm/L	

Pharmacology

Site and mode of action :

Haemacel is pharmacologically inert.

1. Effect on extracellular fluid volume : Following intravenous administration, Haemacel is distributed between intravascular and extravascular compartments. Fluid is not drawn from the extravascular compartment and the increase in intravascular volume will never exceed the volume of Haemacel infused.

The higher molecular weight fractions are retained in the intravascular compartment and excreted more slowly. In surgical patients with varying degrees of blood loss and renal efficiency, the intravascular half life of Haemacel has been established to be 4-6 hours.

2. Effect on Renal Function : Increases in glomerular filtration rate and renal plasma flow as well as a decrease in renal vascular resistance have been observed after Haemacel.

Patients in shock demonstrate a marked increase in diuresis after Haemacel infusion. No effect on serum sodium and potassium levels has been observed, despite an increase in excretion of the electrolytes.

3. Effect on coagulation and fibrinolysis : Haemacel in large or repeated doses has not exhibited any interference with haemostatic mechanisms in vivo.

4. Effect on blood-grouping, cross-matching and blood sedimentation rate: There is no evidence that Haemacel infusions are likely to interfere with blood-typing or cross-matching, even if fast tests are used.

Pharmacokinetics

Absorption : Haemacel is administered by intravenous infusion.

Metabolism : In vitro, it has been demonstrated that gelatin and Haemacel-polygeline similarly, are broken down into small peptides and amino acids by proteolytic enzymes such as trypsin, plasmin or cathepsin. It is assumed that the same processes apply in vivo.

Distribution and Excretion : Following intravenous infusion of 500 mL Haemacel the intravascular distribution is completed after a few circulatory passages and followed by an elimination phase with a half-life of approximately 8 hours. The apparent volume of distribution is 8 litres (12 L/ 100 kg body wt). Excretion proceeds at a non dose-dependent rate and the main route of excretion is renal (80 %). Intestinal excretion and metabolic breakdown do also occur to a smaller extent.

The elimination half-life from the blood appears to vary according to different investigators from 5 hours to 8 hours.

Increase in intravascular volume immediately after infusion will be of the order of 350 mL or 500 mL following the administration of 500 mL or 1 000 mL of Haemacel respectively.

The elimination half-life is increased by age, and by the presence of severely impaired renal function. The excretion is slower in patients with blood loss than in normal volunteers.

Two hours after the infusion of 500 mL Haemacel around 30 % has been excreted, after 24 hours 49 - 59%, and after 48 hours 50 %, or 47 - 65 % depending on the study. Accumulation does not occur.

Two hours after administration of labelled polygeline approximately 3 % has been traced in the form of CO₂ in expired air, indicating metabolism.

Indications

1. Prevention or treatment of shock associated with reduction in effective circulating blood volume due to:
 - Haemorrhage (visible, concealed).
 - Loss of plasma (burns, peritonitis, pancreatitis, crush injuries).
 - Loss of water and electrolytes from persistent vomiting and diarrhoea.
2. As a plasma substitute in surgery where controlled haemodilution is employed.
3. Procedures involving extra-corporeal circulation.
4. Carrier for insulin infusion.
5. Isolated organ perfusion.

Contraindications

Known hypersensitivity to constituents of Haemaccel. Existing anaphylactic/ anaphylactoid reactions.

Precautions

Haemaccel has been associated with rare but severe reactions similar to anaphylaxis. Patients should be monitored carefully for relevant symptoms and signs so that product infusion can be stopped and appropriate urgent treatment commenced.

Rare cases of anaphylactoid reactions have been reported, with bronchospasm, tachycardia, severe hypotension and life-threatening shock. Angioedema* has also been reported in such instances. Patients should be monitored carefully for relevant symptoms and signs so that the product infusion can be stopped and appropriate urgent treatment commenced. These effects seem more likely to occur when Haemaccel is infused rapidly into patients with normovolaemia. These reactions are due to histamine release and may be the result of the cumulative effect of histamine-releasing drugs (see Interactions). They are not true anaphylactic reactions on an immunological basis. If side-effects occur, the infusion should be discontinued immediately. If necessary, treatment should be given (see Adverse Reactions).

Infuse clear solutions only. Once the bottle is opened, the solution should be used immediately. Any unused contents should be discarded, since Haemaccel contains no preservative.

For technical reasons there is a residual air volume in the container. Thus, pressure infusions with the plastic infusion bottle must be carried out under controlled conditions only, as the risk of an air embolism cannot be excluded.

Very rare cases of air embolism have been reported, therefore it is recommended to expel air prior to infusion under pressure (see Dosage and Administration).

Rapid infusion of Haemaccel may stimulate release of histamine. Urticaria and rarely bronchospasm and hypotension may occur. (See Adverse Reactions).

Administration of red cell concentrate or whole blood is required where blood losses exceed 25 % of the blood volume or when haematocrit falls below 25 % by volume.

In the presence of cardiac insufficiency, hypertension, cardiogenic shock, pulmonary oedema, oesophageal varices, haemorrhagic diathesis or anuria, the infusion of Haemaccel should be made only with proper controls because haemodilution or an increase in intravascular/interstitial

fluid volume may be hazardous in these conditions. Blood losses up to 25 % of the blood volume can be replaced by Haemacel alone.

Care should be taken when Haemacel is given to patients with known allergic conditions such as asthma, to patients with a history of histamine response or to patients who have received a histamine releasing drug (See Interactions) within 7 days prior to Haemacel administration, as these patients are probably at an increased risk of histamine release. In such cases, Haemacel may be given only after the prophylactic use of H1 and H2 receptor antagonists.

Haematocrit should not be allowed to fall below 25 % by volume during therapy. If this happens, the administration of red cell concentrate or whole blood must be considered.

The infusion of Haemacel may result in a temporary increase in the erythrocyte sedimentation rate.

Due to the calcium content of Haemacel, the serum calcium concentrations may be found to be slightly elevated for a temporary period, especially when large amounts of Haemacel are administered by rapid infusion. So far, no reports have been received of cases involving clinical signs of hypercalcaemia resulting from an infusion of Haemacel.

Care should be taken if large amounts of Haemacel are infused as haemodilution can lead to decreased coagulation potential.

Use in pregnancy and lactation:

Haemacel, for its usual indications, is not contra-indicated in pregnancy. However, particular care should be exercised when fluid or volume replacements are administered during or immediately after pregnancy.

It is not known whether polygeline is excreted in breast milk. Haemacel is employed during and following labour and no harmful effects on the newborn have been reported.

Interactions with other drugs:

Citrated (conserved) blood should not be mixed with Haemacel or transfused immediately before or after Haemacel using the same venous access, since the Ca⁺⁺ content of Haemacel will cause recalcification. However, citrated blood can be transfused into a separate venous access from that of Haemacel. Haemacel and heparinized blood can be mixed freely.

A decrease in blood pressure caused by the cumulative effects of histamine releasing drugs (anaesthetics, muscle relaxants, analgesics, ganglia blockers, and anticholinergics) is not an indication for rapid infusion of Haemacel.

Paradoxical hypotension has been reported to occur in patients receiving gelatine based plasma volume expanders concurrently with ACE inhibitors, particularly in association with albumin. Paradoxical hypotension has been shown in animal models to occur from the infusion of gelatine based products contaminated with a substance capable of causing the formation of bradykinin in vivo. The level of such substances is currently kept under a critical limit in Haemacel by testing during production. Haemacel should be used with caution in patients receiving ACE inhibitor medication, particularly in association with albumin.

If cardiac glycosides are being given simultaneously, attention must be paid to the synergistic effect of the calcium in Haemacel.

Adverse Reactions

During or after the infusion of any volume-expanding solution, there may be side-effects of varying intensity. Transient skin reactions (urticaria, wheals), hypotension, tachycardia, bradycardia, nausea/vomiting, dyspnoea, rises in temperature and/or chills may occasionally occur. Also, rare cases of anaphylactoid reactions have been reported, with bronchospasm, tachycardia, severe hypotension and life-threatening shock (see Precautions). Angioedema has also been reported in such instances.

During administration of polygeline infusion under pressure, very rare cases of air embolism have been reported.

Management of severe anaphylactic and anaphylactoid reactions:

Cease administration of Haemaccel immediately

Administer oxygen by face mask at 6-8L/min.

- Adults – inject adrenaline 1:1000 IM

small adults	(<50kg)	0.25mL
average adults	(50 – 100kg)	0.50mL
large adults	(>100kg)	0.75mL
- Children (to age 12)
Use adrenaline 1:10 000
Or
Dilute 1 ampoule (1mL) of adrenaline 1:1000 with 9mL water for injection or normal saline

Inject intramuscularly 0.25mL per year of age (approximates to 5 µg/kg)

Establish one, or preferably two, wide bore intravenous lines (16 gauge or larger). Commence rapid fluid resuscitation with normal saline, etc.

If there is severe laryngospasm, bronchospasm, circulatory shock or coma, intubate the trachea and commence intermittent positive pressure ventilation.

If there has been little or no response to the initial intramuscular dose of adrenaline, administer the same dose slowly into the intravenous line. Repeat at 5 minute intervals depending on response. If the patient remains shocked, start an adrenaline infusion (preferably via a central venous line), commencing at 0.25 µg/kg/min and titrating as required to restore blood pressure. Large doses of adrenaline may be needed.

Dosage and Administration

Haemaccel is administered intravenously, and can be infused immediately. If infused under pressure, expel air prior to infusion (see Precautions).

Adults

1. Prevention or treatment of shock associated with reduction in effective circulating blood volume due to:
 - Haemorrhage

Blood loss up to 1500 mL - correct by use of Haemaccel alone.

Blood loss in the range 1500 - 4000 mL - recommended ratio Haemaccel/whole blood is 1:1.

Blood losses above 4000 mL - recommended ratio Haemaccel/whole blood is 1:2.

The rate of infusion and total dose employed will be governed by clinical assessment. In acute situations of severe rapid blood loss, large volumes and rapid infusion may be required. The haematocrit should not be permitted to fall below 25 to 30 % volume during therapy.

- Relative hypovolaemia

Normovolaemia and a high speed of Haemaccel infusion are considered as factors contributing to anaphylactoid reactions in susceptible individuals.

Where Haemaccel is used to restore circulating blood volume in the absence or loss of intravascular fluid, the patient should be carefully observed for skin reactions, difficulty in breathing or precipitous fall in blood pressure.

- Burns

The management of extensive burns should be undertaken by specialised units. The volume of Haemaccel and crystalloid given should be varied according to the clinical response of the patient and the assessment of renal function.

- Water and electrolytes

Haemaccel may be used to restore deficiencies in circulating blood volume in conditions such as persistent vomiting and diarrhoea.

2. As a plasma substitute in controlled haemodilution

Haemaccel has been employed in autologous blood transfusion and haemodilution techniques involving the collection of two or three units of patients' blood just prior to surgery; 2 - 3 units of blood are withdrawn from patients after the induction of anaesthesia for major vascular surgery, each unit being simultaneously replaced by 500 mL of Haemaccel. During the operation, blood losses are immediately replaced with an equal volume of Haemaccel, as long as the haematocrit is above 0.25 -0.30, or with blood alone when the haematocrit falls below this level.

3. Procedures involving extracorporeal circulation

Silvay et al. (1968) recorded very favourable results using a mixture of heparin stabilised whole blood and Haemaccel for filling the pump oxygenator used in conjunction with cardiac surgery in a series of 45 patients. 500 - 2 000 mL of Haemaccel were used in each instance. Merikallio (1976) used a Haemaccel/physiological saline/bicarbonate solution to prime the heart/lung machine for 40 patients undergoing cardiac surgery with cardio-pulmonary bypass. 1 000 mL of Haemaccel were used for each operation.

Isbister (1977) lists Haemaccel as possible fluid replacement for patients undergoing plasmapheresis. The infusion rate used varies from 20 - 80 mL/min, depending on haematocrit, viscosity and total extracorporeal pumping volume per minute.

Stellon and Moorhead (1981) used Haemaccel alone as a replacement fluid in several patients undergoing plasma exchange involving the removal of 2.5 L of plasma. They concluded from their observations of total protein, albumin and globulin, that for patients on

weekly plasma exchange no plasma protein fractions need be administered. Hamilton et al. (1980) recorded the use of plasma protein fraction/ Haemacel/ physiological saline for plasma exchange in a patient with SLE.

4. Carrier Solution for insulin infusion.

Haemacel can be employed when using low dose continuous infusion insulin therapy for the treatment of diabetic coma. Haemacel, added to the infusion fluid before the addition of insulin, minimises absorption of insulin onto glassware and plastic and allows a constant delivery rate to be maintained. Concentrations of polygeline as low as 0.5 % (100 mL Haemacel with 500 mL infusion solution), are effective for this purpose.

5. Isolated Organ Perfusion.

Work in this field has, to date, been carried out only in isolated animal organs. Solutions containing 50% Haemacel have been used for the perfusion of rabbit hearts. Haemacel plus heparin, magnesium and glucose have been used for the perfusion of rat livers.

Paediatric

As for Adult above.

Geriatric

As for Adult above.

With impaired hepatic function

No modification necessary.

With impaired renal function

Haemacel has a beneficial effect on renal function and no exacerbation of pre-existing renal disease need be expected.

Compatibility

Provided sterile precautions are observed, Haemacel may be mixed with ordinary infusion fluids (saline, glucose, Ringer's solution, etc.) and with drugs acting on the cardiovascular system, corticosteroids, muscle relaxants, barbiturates, vitamins, streptokinase and antibiotics of the penicillin series, provided they are water-soluble. Citrated blood (stored blood for transfusion) must not be mixed with Haemacel (because the calcium ions in Haemacel would cause recalcification). However, it may be transfused into a separate venous access from that of the infusion of Haemacel. There is no objection to mixing heparinized blood with Haemacel. In common with all infusion fluids, Haemacel - for physiological reasons - should not be administered at a low temperature.

Overdosage

Haemacel does not lead to a substance-specific impairment of coagulation or platelet function. However, if large amounts of Haemacel are infused, haemodilutional effects on blood coagulation or on platelet function might occur. Therefore, circulatory parameters should be monitored closely.

Medicine Classification

General Sales Medicine

Package Quantities

Haemacel is available in flexible plastic infusion bottles each containing 500 mL of a 3.5 % colloidal solution of polygeline

Storage and shelf life

As proved by viscosity measurements freezing and thawing does not cause any change in the physico-chemical properties. Recommended storage is below 25°C and shelf-life, three years from date of manufacture.

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