Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

EquiHes 60 mg/ml solution for infusion, Ecobag

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml contains:

Hydroxyethyl starch (HES)	60.0g
(Molar substitution:	0.42)
(Average molecular weight:	130,000Da)
Sodium chloride	6.25g
Potassium chloride	0.30g
Calcium chloride dihydrate	0.37g
Magnesium chloride hexahydrate	0.20g
Sodium acetate trihydrate	3.27g
L-Malic acid	0.67g

Electrolyte concentration:

Sodium	140 mmol/l
Potassium	4.0 mmol/l
Calcium	2.5 mmol/l
Magnesium	1.0 mmol/l
Chloride	118 mmol/l
Acetate	24 mmol/l
L-Malate	5.0 mmol/l

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless, aqueous solution

pH:	5.6–6.4
Theoretical osmolarity:	296 mOsmol/l
Acidity (titration to pH 7.4):	<2.0 mmol/l

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. (see sections 4.2, 4.3 and 4.4).

4.2 Posology and method of administration

Posology
Use of Hydroxyethyl starch should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h.

The daily volume and the infusion rate depend on the amount of blood lost and how much fluid is required to restore haemodynamic parameters.
The first 10-20 ml should be infused slowly and under careful monitoring of the patient so that any anaphylactic/anaphylactoid reaction can be detected as early as possible.

The volume limitations given by the degree of haemodilution should be observed, see sections 4.4 and 4.8.

Adults
Maximum daily volume:
The maximum daily dose is 30 ml/kg body weight (BW) (equivalent to 1.8 g Hydroxyethyl starch perkg BW). This is equivalent to 2100 ml EquiHes 60 mg/ml for a patient weighing 70 kg.

Maximum infusion rate:
The maximum infusion rate depends on the clinical situation. Patients in acute shock canbe given up to 20 ml per kg BW per hour (equivalent to 0.33 ml per kg BW per min or 1.2 g Hydroxyethyl starch per kg BW per hour).

In life-threatening situations, 500 ml can be administered rapidly as a pressure infusion. See also section 4.2-Method of administration.

The lowest possible effective dose should be applied. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The maximum recommended daily dose must not be exceeded.

Elderly patients
See section 4.4.

Paediatric population
Data are limited in children therefore it is recommended not to use Hydroxyethyl starch products in this population.

Method of administration
Intravenous use.

In the case of a rapid infusion under pressure, using plastic container with air space inside, the container and infusion set should be emptied of air before the infusion is started. This is to avoid the risk of air embolism that might otherwise be associated with the infusion.

4.3 Contraindications

- hypersensitivity to the active substances or to any of the other excipients listed in section 6.1
- sepsis
- burns
- renal impairment or renal replacement therapy
- intracranial or cerebral haemorrhage
- critically ill patients (typically admitted to the intensive care unit)
- hyperhydration
- pulmonary oedema
- dehydration
- hyperkalaemia

- severe hypernatraemia or severe hyperchloraemia
- severely impaired hepatic function
- congestive heart failure
- severe coagulopathy
- organ transplant patients

4.4 Special warnings and precautions for use

Because of the risk of allergic (anaphylactic/ anaphylactoid) reactions, the patient should be monitored closely and the infusion instituted at a low rate. (See section 4.8).

The indication for volume replacement with Hydroxyethyl starch has to be considered carefully, and haemodynamic monitoring is required for volume and dose control. (See also section 4.2.)

Volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary and cardiocirculatory problems. Serum electrolytes, fluid balance and renal function should be monitoredclosely. Electrolytes and fluids should be substituted according to individual requirements.

Hydroxyethyl starch products are contraindicated in patients with renal impairment or renal replacement therapy (see section 4.3). The use of Hydroxyethyl starch must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after Hydroxyethyl starch administration. Monitoring of renal function in patients is recommended for at least 90 days.

Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders.

Severe haemodilution resulting from high doses of Hydroxyethyl starch solutions must also be avoided in the treatment of hypovolaemic patients.

In the case of repeated administration, blood coagulation parameters, should be monitored carefully. Discontinue the use of Hydroxyethyl starch at the first sign of coagulopathy.

In patients undergoing open heart surgery in association with cardiopulmonary bypass the use of Hydroxyethyl starch products is not recommended due to the risk of excess bleeding.
Sufficent fluid intake must be ensured.

Elderly patients
Elderly patients, who are more likely to suffer from cardiac insufficiency and renal impairment, should be closely monitored during treatment, and the dosage should be carefully adjusted, in order to avoid cardiocirculatory and renal complications resulting from hypervolaemia.

Surgery and trauma:
There is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long term safety. Other available treatment options should be considered.

Paediatric population:
Data are limited in children therefore it is recommended not to use Hydroxyethyl starch products in this population. (see section 4.2)

Influence on laboratory tests
Transiently raised alpha-amylase levels can occur after administration of solutions with Hydroxyethyl starch. This should not be interpreted as a sign of pancreatic injury (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides
The adverse effects of aminoglycosides on kidneys may be increased in combination with Hydroxyethyl starch infusions.

Medicinal products causing potassium or sodium retention
Consideration should be given to the concomitant administration of medicinal products that can cause potassium or sodium retention.

Digitalis glycosides
Raised calcium levels can increase the risk of toxic effects of digitalis glycosides.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Hydroxyethyl starch in pregnant women. Animal reproduction toxicity studies with similar products have revealed vaginal bleeding, embryotoxicity and teratogenicity after repeated treatment in test animals (see section 5.3).

Harmful effects on the foetus can occur with Hydroxyethyl starch-related anaphylactic/anaphylactoid reactions in treated pregnant women.
EquiHes 60 mg/ml should be used during pregnancy only if the potential benefits outweigh the possible risks to the foetus. This should be borne in mind in particular if treatment with EquiHes 60 mg/ml is being considered during the first trimester.

Special care must be taken to avoid overdose resulting in hypervolaemia with consecutive pathological haemodilution and foetal hypoxia (see section 5.3).

Breastfeeding
It is not known whether Hydroxyethyl starch passes into breast milk, caution should be exercised on administration to breast-feeding women. The temporary cessation of breast-feeding may be considered.

Fertility
No data available

4.7 Effects on ability to drive and use machines

This medicinal product has no influence on the ability to drive and use machines.

4.8 Undesirable effects

General
The most common side-effects observed are directly related to the therapeutic effect of starch solutions and the volume given, i.e. dilution of the blood as a result of the filling of the intravascular space without administering blood components at the same time. Coagulation factor dilution can also occur. Serious anaphylactic/anaphylactoid reactions have been reported and may require immediate action (please refer also to the section ‘Anaphylactic/Anaphylactoid reactions’ below).

	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)**	**Frequency not know (cannot be estimated from the available**

					data)
Blood and lymphatic system disorders	Decreased haematocrit, reduced concentration of plasma proteins	Dilution of coagulation factors, prolongation of bleeding time and aPTT, reduced level of FVIII/vWF complex (1) (see section 4.4)			
Hepatobiliary disorders					Hepatic injury
Immune system disorders				Anaphylactic/Anaphylactoid reactions of various degrees (see " Anaphylactic/Anaphylactoid reactions" below)	
Renal and urinary disorders					Renal injury
General disorders and administration site conditions			Itching which responds poorly to any therapy (2)		
Investigations	Increased serum α-amylase levels (3)				

(1) Effects occur after administration of relatively large volumes of Hydroxyethyl starch and can affect blood coagulation. See section 4.4.

(2) This itching can occur several weeks after the end of the starch infusions and can persist for months. The probability of this undesirable effect has not been sufficiently studied for EquiHes 60 mg/ml.

(3) This effect is a result of the formation of an amylase complex of Hydroxyethyl starch with delayed renal and extrarenal elimination. This should not be misinterpreted as evidence of a pancreatic disorder.

Anaphylactic/Anaphylactoid reactions
After administration of Hydroxyethyl starch, anaphylactic/anaphylactoid reactions of various degrees can occur which are not dose dependant. Therefore, all patients receiving starch infusion should be monitored closely for anaphylactic/anaphylactoid reactions. In the event of an anaphylactic/anaphylactoid reaction, the infusion should be discontinued immediately and the usual acute treatment initiated.

It is not possible to predict by tests which patients may be expected to suffer an anaphylactic/anaphylactoid reaction nor is it possible to predict the course and severity of such a reaction. Prophylaxis with corticosteroids has not been shown to have a preventive effect.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms
Overdose with EquiHes would lead to unintended 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).

Treatment
In this case, the infusion must be discontinued immediately and administration of diuretics considered. If an overdose occurs, the patient should be treated symptomatically and electrolytes should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitute and plasma proteins,
ATC code: B05A-A07

Mechanism of action, pharmacodynamic effects
EquiHes is a colloidal plasma volume substitute containing Hydroxyethyl starch in a balanced electrolyte solution. The average molecular weight is 130,000 Daltons and its molar substitution is 0.42.

EquiHes 60 mg/ml is iso-oncotic, i.e. the increase in the intravascular plasma volume is equivalent to the infused volume.

With isovolaemic administration, the volume expanding effect persists for at least 4-9 hours. The duration of the volume effect is primarily based on molar substitution and to a lesser extent on the average molecular weight. Intravascular hydrolysis of Hydroxyethyl starch polymers results in a continuous release of smaller molecules which also are oncotically active before they are excreted via the kidneys.

EquiHes 60 mg/ml may lower the haematocrit and the plasma viscosity.

EquiHes also has a favourable effect on the microcirculation by altering the flow characteristics of the blood.

The cation pattern in the crystalloid component of EquiHes 60 mg/ml is adapted to physiological plasma electrolyte concentrations. The anion pattern is a combination of chloride, acetate and malate, the purpose of which is to minimise the risk of hyperchloraemia and acidosis. Additions of acetate and malate instead of lactate anions are intended to reduce the risks of lactic acidosis.

5.2 Pharmacokinetic properties

General
The characteristics of the electrolytes contained in EquiHes are the same as in normal physiology.

<u>Absorption</u>
As EquiHes is administered intravenously, the bioavailability is 100%.

Distribution
Hydroxyethyl starch is a mixture of several different molecules with a different molecular weight and degree of substitution. Like all colloids, Hydroxyethyl starch, too, is temporarily stored particularly in the cells of the mononuclear phagocyte system (MPS), however, without producing any irreversible toxic effects on liver, lungs, spleen and lymph nodes. Minor quantities of the stored active substance in the skin are still histologically detectable several months after administration. Such storage phenomena are assumed to be the cause for the itching that has been observed after long-term administration of high doses of Hydroxyethyl starch.

Hydroxyethyl starch does not pass the blood-brain barrier. No relevant Hydroxyethyl starch concentrations were detected in the umbilical cord excluding the possibility of a maternal-foetal transfer of Hydroxyethyl starch .

Biotransformation/Elimination
Elimination is dependent on the degree of substitution and to a lesser extent on molecular weight. Molecules which in terms of size are below the so-called renal threshold are excreted by glomerular filtration. Larger molecules are first degraded by alpha-amylase before they are excreted renally. The rate at which the molecules are degraded decreases with increasing degree of substitution of the molecules.

After a single infusion of 1 000 ml EquiHes 60 mg/ml, plasma clearance is 19 ml/min and AUC 58 $mg \times h \times ml^{-1}$. The terminal serum half-life is about 4-5 hours.

Pharmacokinetics in paediatric patients
No pharmacokinetic data from treatment of children are available.

5.3 Preclinical safety data

No toxicological animal studies have been conducted with EquiHes 60 mg/ml.

Published animal toxicological studies with repeated hypervolaemic treatment with similar Hydroxyethyl starch products have revealed bleeding and extensive histiocytosis (accumulation of foam-like histiocytes/macrophages) in several organs with an increase in weight of the liver, kidneys and spleen. Infiltration of fat and vacuolation of organs as well as elevations of plasma AST and ALT have been reported. It has been suggested that some of the effects described were caused by haemodilution, increased circulatory load and uptake and accumulation of starch in phagocytic cells
Similar Hydroxyethyl starch products have been reported to be non-genotoxic in standard tests.

Reproductive toxicity studies of Hydroxyethyl starch products showed vaginal bleeding and signs of embryo-/foetotoxicity and teratogenicity associated with repeated administration to test animals. These effects may be due to haemodilution and result in foetal hypoxia and hypervolaemia. Bleeding can also be in part a direct consequence of the effects that Hydroxyethyl starch has on the blood coagulation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (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
Plastic bag (Ecobag): 2 years

After first opening:
The product should be administered immediately after connecting the container to the administration set.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

EquiHes 60 mg/ml is available in the following types of packaging and contents:

- Plastic bag (Ecobag) made of three-layer laminate (polypropylene inner layer) with butyl rubber closures and polypropylene outer bag.

  20 x 250 ml
  20 x 500 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements for disposal.
Administration should commence immediately after connecting the container to the administration set.
For single use only.
Use as soon as the primary packaging is opened. Any unused contents should be discarded.
Use only if the solution is clear, colourless and the packaging is undamaged.
Do not re-connect partially used containers.

7 MARKETING AUTHORISATION HOLDER

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Carl-Braun-Strasse 1
34212 Melsungen
Germany

Postal address:
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Germany

8 MARKETING AUTHORISATION NUMBER

PA0736/024/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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