IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0736/020/003
Case No: 2052630

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B. Braun Melsungen AG

Carl-Braun Strasse 1, **34212 Melsungen**, **Germany**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Venofundin 60mg/ml solution for infusion, Ecobag

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/12/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Venofundin 6% w/v solution for infusion, Ecobag

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml contains

Poly(O-2-hydroxyethyl)starch (HES)	60.0 g
(Molar substitution:	0.42)
(Mean molecular weight:	130,000 Da)
Sodium chloride	9.0 g

Electrolyte concentration:

Sodium	154 mmol/l
Chloride	154 mmol/l

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colorless aqueous solution.

pH:	4.0–6.5
Theoretical osmolarity:	309 mOsmol/l
Titration acidity:	<1.0 mmol/l

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of imminent or manifest hypovolaemia and shock.

4.2 Posology and method of administration

The daily dose and infusion rate depend on the extent of blood loss, maintenance or restoration of hemodynamic parameters.

The first 10–20 ml should be infused slowly and with careful patient monitoring so that a possible anaphylactoid reaction can be detected as early as possible.

Maximum infusion rate:
The maximum infusion rate depends on the clinical situation. Patients in acute shock may be administered up to 20 ml per kg of body weight per hour (equivalent to 0.33 ml/kg/min or 1.2 g of hydroxyethyl starch per kg of body weight per hour).

In life-threatening situations, 500 ml may be administered by manual pressure infusion. Also see "Method of administration and duration of therapy".

Maximum daily dose:
Up to 50 ml of Venofundin per kg of body weight (equivalent to 3.0 g of hydroxyethyl starch per kg of body weight). This is equivalent to 3,500 ml of Venofundin for a 70-kg patient.

Paediatric patients:

When Venofundin 60 mg/ml is used in children the dose should be individualised, taking the haemodynamic status and the underlying disease into account. The maximum daily dose of 50 ml/kg bodyweight should not be exceeded. Clinical data reveal that moderate doses of 10 - 20 ml/kg bodyweight/day regardless of age group do not show a different pattern and incidence of undesirable effects than in adults. There is only limited clinical data on the long-term use of Venofundin in children.

Method of administration and duration of therapy:

For intravenous use.

If administration is by rapid infusion under pressure, all air must be withdrawn from the plastic container and infusion set prior to infusion, as otherwise there is a risk of producing air embolism during infusion.

The duration of therapy depends on the duration and extent of hypovolemia, the hemodynamic effects of the administered treatment, and the level of hemodilution.

4.3 Contraindications

– Hyperhydration states including pulmonary edema.
– Renal failure with oliguria or anuria.
– Intracranial bleeding.
– Severe hypernatremia or severe hyperchloremia.
– Hypersensitivity to hydroxyethyl starch or to any of the excipients.
– Severely impaired hepatic function.
– Congestive cardiac failure.

4.4 Special warnings and precautions for use

Volume overload from overdosage should always be avoided. Dosage should be carefully adjusted, especially in patients with cardiac insufficiency.

Particular caution should be exercised in patients with renal impairment. The dose may need to be adjusted.

Elderly patients with hypovolaemia should be thoroughly monitored, and the dosage should be adapted, in order to avoid impairment of renal function.

Serum electrolytes, fluid balance, and kidney function should be monitored. Adequate fluid intake must be ensured.

Patients with severe dehydration should first receive intravenous electrolyte solutions.

Particular caution should be exercised in patients with hepatic insufficiency and in those with blood coagulation disorders particularly haemophilia and known or suspected v. Willebrand´s disease.

To ensure correct blood typing, a blood sample should be taken prior to the administration of Venofundin.

Because of the possibility of allergic (anaphylactic/anaphylactoïd) reactions, appropriate monitoring of patients is necessary, and a slow infusion rate should be initiated (See section 4.8).

Elevated serum alpha-amylase concentrations may be observed temporarily following administration of HES solutions and must not be considered diagnostic of impaired pancreatic function (See section 4.8).

Venofundin contains 154 mmol/l sodium. This is to be considered for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, no report of interaction with medicinal products has been ceived until now.

4.6 Pregnancy and lactation

No adequate data are available for Venofundin from the treatment of pregnant women. Venofundin has not been tested in reproductive toxicology studies in animals, but studies of similar products have revealed vaginal bleeding, embryotoxic and teratogenic effects after repeated treatment of laboratory animals (see section 5.3). HES-related anaphylactic reactions in treated pregnant women may have harmful effects on the fetus. Venofundin should be used in pregnant women only if the anticipated benefits outweigh the potential risk to the fetus; this is especially to be considered when administration of Venofundin in the first three months of pregnancy is planned.

As it is not known whether the modified starch in Venofundin is excreted in breast milk, caution should be exercised when administering this product to breastfeeding mothers. Temporary interruption of breastfeeding may be considered.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:
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), very rare (≤1/10,000)

The most commonly reported adverse reactions are directly related to the therapeutic effects of starch solutions and the doses administered, *i.e.*, hemodilution resulting from expansion of the intravascular space without concurrent administration of blood components. Dilution of coagulation factors may also occur.

The anaphylactic reactions described below are not dose-dependent.

Blood and lymphatic system disorders
Very common: Reduced hematocrit and decreased plasma protein concentrations as a result of hemodilution.

Common (dose-dependent): Higher doses of hydroxyethyl starch cause dilution of coagulation factors and may thus affect blood clotting. Bleeding time and aPTT may be increased and FVIII/vWF complex levels may be reduced after administration of high doses. See 4.4 "Special warnings and special precautions for use".

Immune system disorders
Rare: Anaphylactic reactions of various intensities may occur after administration of hydroxyethyl starch. All patients receiving starch infusions should therefore be closely monitored for anaphylactic reactions. In case of an anaphylactic reaction, the infusion must be stopped immediately and the usual emergency treatment instituted.
There are no tests to identify patients in whom an anaphylactic reaction is likely, nor can the outcome and severity of such a reaction in a given patient be predicted.

The prophylactic use of corticosteroids has not proved effective.

General disorders and administration site conditions:
Uncommon: Repeated infusions of HES for many days, especially when high cumulative doses are reached, usually lead to pruritus which responds very poorly to therapy. This pruritus may occur many weeks after discontinuing the starch infusions and may persist for months. The likelihood of this adverse effect has not been adequately studied for Venofundin.

Investigations
Very common: The infusion of hydroxyethyl starch produces elevated serum α-amylase concentrations. This effect is the result of the formation of an amylase complex of hydroxyethyl starch with delayed renal and extrarenal elimination. It should not be misinterpreted as evidence of a pancreatic disorder.

4.9 Overdose

The greatest risk associated with an acute overdose is hypervolemia. In this case, the infusion must be stopped immediately, and administration of diuretics be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitutes and plasma protein fractions,
ATC code: B05A A07

Venofundin is a colloidal plasma volume substitute and contains 6% hydroxyethyl starch (HES) in normal saline (sodium chloride 9 mg/ml). Its mean molecular weight is 130,000 Dalton and its molar substitution is 0.42.

Venofundin is isooncotic, *i.e.*, the intravascular plasma volume increase is equivalent to the infused volume.

The duration of the volume effect depends primarily on molar substitution and to a lesser extent on the mean molecular weight. Intravascular hydrolysis of HES polymers results in the continuous release of smaller molecules which are also oncotically active before being excreted via the kidneys.

Venofundin may reduce hematocrit and plasma viscosity.

Following isovolemic administration, the volume-expanding effect is maintained for at least 6 hours.

5.2 Pharmacokinetic properties

Hydroxyethyl starch is a mixture of several molecular species with different degree of substitution and molecular weight. The elimination depends on molecular weight and degree of substitution. Molecules smaller than the renal threshold are eliminated via glomerular filtration. Larger molecules are degraded by α-amylase and are thereafter eliminated renally. The rate of degradation decreases with increased degree of substitution. Approximately 50 % of a given dose is excreted into urine within 24 hours.

Following a single infusion of 1000 ml of Venofundin, plasma clearance is 19 ml/min and the AUC is 58 mg*h/ml, and the terminal serum half-life is about 12 hours.

5.3 Preclinical safety data

Venofundin has not been tested in animal toxicology studies. Published animal toxicology studies of repeated hypervolemic treatment with similar HES products have revealed bleeding and extensive histiocytosis (accumulation of foamy histiocytes/macrophages) in many organs, along with increased liver, kidney, and spleen weights. HES deposits and organ vacuolization have been reported along with elevated plasma ASAT and ALAT levels.

Some of the described effects have been suggested to be due to hemodilution, circulatory overload, and uptake and accumulation of starch in phagocytic cells.

Similar HES products have been reported to be non-genotoxic in standard tests.

Reproductive toxicity studies of HES products showed vaginal bleeding, embryo-foetotoxic and teratogenic effects after repeated administration to laboratory animals.
These effects may be related to hemodilution, leading to fetal hypoxia, and to hypervolemia.
Bleeding may partly also be related to direct effects of HES on the blood coagulation. Hemodilution from volume overload should always be avoided when treating the hypovolemic patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

2 years.

Shelf life after first opening:
The product should be used immediately.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Venofundin is available in the following containers and pack sizes:
10 x 250 ml
20 x 250 ml
10 x 500 ml
20 x 500 ml
10 x 1000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only.

Use only clear solution, practically free from particles, from intact containers.

Use immediately after first opening

7 MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Strasse 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA 736/20/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 August 2006
Date of last renewal: 17 December 2009

10 DATE OF REVISION OF THE TEXT

January 2010