IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0167/133/001
Case No: 2078023

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

Baxter Healthcare Limited

Caxton Way, **Thetford**, **Norfolk IP24 3SE**, **United Kingdom**

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

Plasma Volume Redibag 6 % Solution for Infusion

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 **20/04/2010** until **12/11/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Plasma Volume Redibag 6 % Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000ml contains:	
Poly(O-2-hydroxyethyl) starch (HES)	60.0g
(Molar substitution:	0.42)
(Mean molecular weight:	130 000 Da)
Sodium chloride	6.00g
Potassium chloride	0.400g
Calcium chloride dihydrate	0.134g
Magnesium chloride hexahydrate	0.200g
Sodium acetate trihydrate	3.70g
Electrolyte concentration:	
Sodium	130 mmol/l
Potassium	5.36 mmol/l
Calcium	0.912 mmol/l
Magnesium	0.984 mmol/1
Chloride	112 mmol/l
Acetate	27.2 mmol/l
pH:	5.0–7.0
Theoretical osmolarity:	277 mOsmol/l (approx)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless, aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of imminent or manifest hypovolaemia and hypovolaemic 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 haemodynamic parameters, and the level of haemodilution.
The first 10–20 ml should be infused slowly and with careful patient monitoring so that possible anaphylactoid reactions can be detected as early as possible.

Maximum infusion rate:
The maximum infusion rate depends on the clinical situation. Patients in acute hypovolaemic shock may be administered up to 20 ml per kg body weight per hour (equivalent to 0.33 ml/kg body weight/min or 1.2 g hydroxyethyl starch per kg body weight per hour).
In life-threatening situations 500 ml may be administered by pressure infusion. See "*Method of administration and duration of therapy*".

Maximum daily dose:
Up to 50 ml Plasma Volume Redibag per kg body weight (equivalent to 3.0 g hydroxyethyl starch, 6.5 mmol sodium and 0.268 mmol potassium per kg body weight). This is equivalent to 3,500 ml Plasma Volume Redibag for a patient weighing 70 kg.

Method of administration and duration of therapy:

Infusion solution for intravenous administration.

In life-threatening situations, 500 ml as a rapid infusion (under pressure). Before pressure infusion, complete venting of the infusion bag and infusion set must be guaranteed.
The infusion rate will usually be lower for selected peri-operative indications, in the case of burns and septic shock.

The duration of infusion will depend on the degree of hypovolaemia and the haemodynamic response.

Treatment of children:
Regarding use in children, see sections 4.4 and 5.1.

The dosage in children should be adjusted in accordance with the individual colloid requirement, taking into account underlying diseases, haemodynamic conditions, urine production and fluid status.

4.3 Contraindications

- Hyperhydration states, including pulmonary oedema and congestive heart failure
- Renal failure with oliguria or anuria
- Intracranial bleeding
- Known hypersensitivity to hydroxyethyl starch or any of the excipients (see 6.1)
- Severely impaired hepatic function

4.4 Special warnings and precautions for use

Special precaution should be exercised in:
Hypernatraemia
Hyperchloraemia
Hyperkalaemia (e.g. adrenocortical insufficiency, extensive tissue destruction)

Volume overload caused by over-infusion should always be avoided. The infusion volume should be carefully balanced, particularly in patients with underlying cardiac insufficiency.

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

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

Patients with severe dehydration should first receive an intravenous infusion with a suitable electrolyte solution.

Caution in patients with diseases that require a restricted sodium intake (heart failure, generalised oedema, hypertension, eclampsia).

Particular caution should be exercised in patients with hepatic insufficiency and in those with severe blood coagulation disorders particularly haemophilia and Von Willebrand's disease. When using a high dose or repeated administration of hydroxyethyl starch regular monitoring of haemostasis is recommended by measuring APTT and possibly Factor VIII in order to detect Von Willebrand's disease.

Repeated, prolonged administration of high molecular weight HES has caused accumulation of HES in the liver. This has led to impaired liver function and portal hypertension in patients with chronic liver disease.

In metabolic alkalosis and clinical situations where alkalinisation should be avoided, saline based solutions containing HES 130/0.4 in 0.9% sodium chloride solution should be preferred over alkalising solutions like Plasma Volume Redibag.

In general, a significant blood dilution may make the results of blood typing difficult to interpret. A blood sample could be taken prior to administration of large volumes of hydroxyethylstarch containing products to ensure correct blood typing.

Because of the possibility of allergic (anaphylactic/anaphylactoid) 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 should not be considered diagnostic of impaired pancreatic function (see section 4.8).

Clinical studies for Plasma Volume Redibag in children have not been performed. However, a few clinical trials have been performed with HES products in children. If Plasma Volume Redibag is used in children the dose should be carefully defined keeping the best patient's benefit/risk ratio in mind, taking into account the haemodynamic status and the underlying disease.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of HES products may increase the clotting time in patients treated with heparin, anticoagulants, NSAIDs and sodium valproate.
Owing to the risk of microbial contamination and incompatibility, Plasma Volume Redibag should not be mixed with other medications. If the addition of any other drug is indicated in an individual case, it is important to take note of general compatibility. Mixing Plasma Volume Redibag, particularly with solutions containing phosphate or carbonate, can result in precipitation.

4.6 Pregnancy and lactation

There is insufficient information available about the treatment of pregnant women with Plasma Volume Redibag. It has not been tested in reproduction toxicology animal studies, but vaginal bleeding, embryotoxic and teratogenic effects were seen in animal experiments after repeated administration of similar products (see 5.3.).

HES-related anaphylactic reactions in pregnant women might have harmful effects on the foetus.

As a result, Plasma Volume Redibag should only be used in pregnant women if the foreseeable benefit outweighs the potential risks to the foetus. This must be taken into account, especially if administration of Plasma Volume Redibag during the first three months of pregnancy is planned.

It is unlikely that hydroxyethyl starch will be administered during breast feeding and it is unknown whether hydroxyethyl starch is excreted in human breast milk. The excretion of hydroxyethyl starch in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Plasma Volume Redibag should be made taking into account the benefit of breast-feeding to the child and the benefit of Plasma Volume Redibag therapy to the woman.

4.8 Undesirable effects

Assessment of adverse reactions is based on the following frequency rates: *very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data)..*
The most commonly reported adverse reactions are directly related to the therapeutic effects of starch solutions and the doses administered, e.g. haemodilution resulting from expansion of the intravascular space without concurrent administration of blood components. Dilution of coagulation factors may also occur.
Very rare hypersensitivity reactions are not dose-dependent.

Blood and the lymphatic system disorders
Very common: Decreased haematocrit and reduced plasma protein concentration as a result of haemodilution.

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

Immune system disorders
Rare: Anaphylactic reactions of varying intensity. See “Anaphylactic reactions”.

General disorders and administration site conditions
Uncommon: Repeated infusion of HES for many days, especially if high cumulative quantities are reached, usually lead to pruritus which responds very poorly to therapy. This pruritus may appear several weeks after the end of the starch infusions and may persist for months. The likelihood of this adverse effect has not been adequately studied for Plasma Volume Redibag.

Investigations
Very common: The infusion of hydroxyethyl starch produces elevated serum concentrations of α-amylase. This effect is the result of the formation of an amylase complex of hydroxyethyl starch with delayed renal and extrarenal elimination. This effect should not be misinterpreted as evidence of a pancreatic disorder.
The elevation of the serum α-amylase concentration will disappear 3 – 5 days after administration.

Anaphylactic reactions
Anaphylactic reactions of varying intensity may occur after administration of hydroxyethyl starch. All patients receiving starch infusions should therefore be closely monitored for anaphylactic reactions. Similarly, the outcome and severity of any such reaction cannot be predicted for any given patient. In the case of an anaphylactic reaction, the infusion must be stopped immediately and suitable emergency measures instituted.

There are no specific tests enabling patients who are likely to suffer an anaphylactic reaction to be identified. Equally the outcome and the severity of any such reaction cannot be predicted for the patient.
Hepatic dysfunction, that may be caused by starch accumulation, has been observed with other HES products.

The prophylactic use of corticosteroids has not proved effective.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions,
ATC Code: B05A A07

Plasma Volume Redibag is a colloid plasma substitute and contains 6% hydroxyethyl starch in Ringer's acetate solution (theoretical osmolarity 277 mOsm/l). The mean molecular weight is 130,000 Dalton, molar substitution is 0.42.

Plasma Volume Redibag is iso-oncotic, i.e. the intravasal volume increase is equivalent to the infused volume.

The electrolyte component in Plasma Volume Redibag is Ringer's acetate solution with an iso-ionic cation composition and with acetate as a metabolising anion. Acetate is oxidised and has an alkalising effect in the acid-base balance which is advantageous where there is an underlying tendency to metabolic acidosis.

Plasma Volume Redibag combines the colloid HES 130/0.42 for volume replacement and a balanced acid-base component, Ringer's acetate solution.

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

Haemodilution with Plasma Volume Redibag may reduce haematocrit and plasma viscosity.

Following isovolaemic haemodilution, the volume-expanding effect is maintained for at least 6 hours.

Experience from treatment of children
Clinical studies for Plasma Volume Redibag in children have not been performed. The experience from treatment of children with HES 130/0.4 is limited. According to data from scientific literature in infants and toddlers (n=41) undergoing non-cardiac surgery, a mean dose of 16ml/kg (HES 130/0.4) was administered for the purpose of haemodynamic stabilisation and tolerated safety. In a second trial, 21 children (between 6 and 72 months of age) undergoing cardiac surgery tolerated a fixed dose of 10ml/kg without complications.

If Plasma Volume Redibag is used in children the dose should be individualised, taking the haemodynamic status and the underlying disease into account. No pharmacokinetic data from the treatment of children is available.

5.2 Pharmacokinetic properties

Hydroxyethyl starch is a mixture of various substances with different degrees of substitution and molecular weights. Elimination depends on the molecular weight and the degree of substitution. Molecules below the renal threshold are eliminated by 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 the dose administered is excreted with the urine within 24 hours.

Following a single infusion of 1000 ml Plasma Volume Redibag, plasma clearance is 16 ml/min and the AUC is 51 mg/ml/h. The terminal half-life is about 17 hours.

5.3 Preclinical safety data

Plasma Volume Redibag has not been tested in toxicology studies in animals. In published toxicology studies in animals involving repeated hypervolaemic use of similar HES products, bleeding and pronounced histiocytosis (accumulation of foam cells/macrophages) was seen in many organs, accompanied by increased liver, kidney and spleen weights. Fat deposits and organ vacuolisation were also reported, together with raised plasma levels of AST and ALT. It is assumed that a few of the described effects are attributable to haemodilution, circulatory overload and absorption and accumulation of starch in phagocytes.

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

In reproduction toxicology studies in animals, vaginal bleeding, embryotoxic and foetotoxic as well as teratogenic effects were seen after repeated administration of HES products. These effects might be connected with haemodilution, which leads to foetal hypoxia, and with hypervolaemia. The bleeding might also be partly related to direct effects of HES on blood coagulation. Haemodilution caused by volume overload should always be avoided when treating hypovolaemic patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections,
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Incompatibilities can occur when Plasma Volume Redibag is mixed with other medications, especially solutions containing phosphate or carbonate.

In absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Polypropylene infusion bag with butyl rubber stopper and polypropylene outer bag
10 x 500 ml

6.6 Special precautions for disposal and other handling

Use bag unvented.
For single use only.
Use immediately after first opening and discard any unused product.
Use only clear solution, practically free from particles, from intact containers.

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

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford
Norfolk
IP24 3SE
UK

8 MARKETING AUTHORISATION NUMBER

PA0167/133/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th November 2008

10 DATE OF REVISION OF THE TEXT