Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each one litre of solution contains:

Hydroyethyl Starch (Average nominal MW 450,000 DA; molar substitution 0.7)	60.0	g
Sodium Chloride	9.0	g
Osmolarity	310	mOsm/l (approx)
Colloidal oncotic pressure	30	mm Hg (approx)
pH	3.5-7.0	
Na^+	154	mEq/l
$C1^-$	154	mEq/l

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
A clear almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a plasma volume expander for the treatment of hypovolaemia and shock. The solution is not to be used as a substitute for either blood or plasma.

4.2 Posology and method of administration

a) Plasma Volume Expansion
The dose and rate of infusion will depend upon the clinical condition of the patient, the amount of blood lost and the resultant haemoconcentration in the individual patient. Care should be exercised in keeping the dose and rate to the lowest effective level and due to the risk of anaphylactic reactions occurring the initial 10-20ml of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion should be infused slowly, whilst the patient is kept under careful observation.

When administering 6% Hetastarch in 0.9% Sodium Chloride Solution for Infusion it should be appreciated that the effective increase in plasma volume exceeds that of the volume infused (refer to Section 5.1). In adults the amounts usually administered is 500ml to 1000ml. Total dosage does not usually exceed 1500ml per day or 20ml per kg of body weight per day for a typical 70kg patient, but in common with other colloids the limiting dose will depend on circulating volume and haematocrit; in patients without cardiovascular or pulmonary risks the solution should only be used when the haematocrit is greater than 30%. An initial administration rate of not greater than 15 ml/kg/hr is recommended. The total daily dose should not exceed 20 ml/kg.
For routine procedures, administration should not be repeated in the same patient within a period of six months, although there is no pharmacological or clinical evidence to give cause for concern with regard to repeated application.

b) Use in Children

The safety and efficacy of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion has not been established. Therefore the product should not be administered to children below 18 years of age.

c) Use in Elderly

Use in the elderly must be dictated by the pre-existing clinical status of the patient.

4.3 Contraindications

6% w/v Hetastarch in 0.9% Sodium Chloride Solution for Infusion is contraindicated in patients with a known hypersensitivity to the drug and/or any other constituent. Note: the active ingredient is derived from maize starch.
Patients with severe congestive heart failure or cardiac decompensation, thrombocytopaenia and other severe coagulation disturbances, renal failure with oliguria or anuria, pulmonary oedema, intracranial bleeding and severe haemorrhagic disorders.
In addition, patients with a variety of volaemic disorders (dehydration, hyperhydration and hypervolaemia) as well as those with electrolyte disturbances (hypernatraemia and hyperchloraemia). Patients on dialysis since the only way that 6% w/v hetastarch in 0.9% w/v sodium chloride intravenous infusion is eliminated is by glomerular filtration.

4.4 Special warnings and precautions for use

Plasma Volume Expansion

The possibility of circulatory volume overload should always be bourne in mind. In common with all plasma volume expanders, 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion can produce dilutional effects on plasma proteins, fibrinogen and prothrombin activity. In large volumes (>1.5 litres) hetastarch may alter the coagulation mechanism and produce a transient prolongation of the clotting time.

It should be used with caution in patients with severe bleeding disorders or those vulnerable to vascular overloading (congestive cardiac failure, renal disease) since overloading of the circulation with ensuing cardiac distress and pulmonary oedema may occur. In patients with afibrinogenaemia use of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion should be restricted to cases of life threatening emergencies. It should not be used in conjunction with heparin. Isovolaemic substitution with 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion up to 20% of blood volume lost, does not interfere with cross-matching determinations. Higher dilutions may lead to rouleaux formation.
Since an anaphylactic reaction is always possible during infusion of a colloidal solution the first 10-20ml should be infused slowly together with careful monitoring of the patient. It is also recommended that particular attention should be paid to patients who show decreased renal excretion, or suffer from chronic hepatic disease.
It is recommended that the serum electrolytes (particularly sodium, potassium and chloride) together with water balance are regularly monitored. Maintenance of an adequate fluid supply is essential. 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion forms a macro-molecular aggregate with amylase (by which it is degraded) producing a rise in serum amylase levels for up to three days post infusion, which may interfere with blood chemistry determinations, especially with the diagnosis of pancreatitis if determined in this way.
The long term effects of storage of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion in the liver and spleen are unknown. For this reason, use in routine procedures should not be repeated within a period of six months.

4.5 Interaction with other medicinal products and other forms of interaction

Use in conjunction with heparin or oral anticoagulants may prolong the bleeding time, but compatibility has been confirmed with citrate anticoagulant. Special care should be exercised with patients currently taking concomitant medication, in particular β-blockers and vasodilators where changes in systemic blood pressure and heart rate may not be detected despite the re-expansion therapy. The possible interaction with the measurement of a range of serum components (protein, glucose, fatty acids, cholesterol and sorbitol) should be bourne in mind. The nephrotoxicity of aminoglycoside antibiotics may be increased when co-administered with 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion. There is no experience concerning any possible interaction with nutritional products.

4.6 Pregnancy and lactation

The safety of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion for use in human pregnancy has not been established. Reproduction studies have been carried out in mice with no evidence of foetal damage, but are insufficient to assess the safety with respect to the development of the embryo or foetus, the course of gestation and peri and post natal development. The infusion should not be used in pregnant women, particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the potential hazards. The risk of an anaphylactic reaction with subsequent foetal brain damage should be seriously considered when electing to use this product in pregnancy.
The passage of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion into the mother's milk is not known; therefore lactation should be interrupted when administration of the solution is required.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion is non antigenic nor is its administration associated with raised plasma histamine levels. However, following normal infusion rates (see Posology and Method of Administration) a number of mild allergic or sensitivity reactions have occasionally been reported consisting of peri-orbital oedema, urticaria, wheezing and mild influenza-like symptoms. Long lasting itching has also been reported which may not exhibit itself for several days or even weeks following the infusion. Other reactions such as chills, paraesthesiae, headache, weakness, vomiting, skin rashes, submaxillary and parotid gland enlargement, muscle pains and peripheral oedema of the lower extremities have been reported. If such reactions occur they are readily controlled by discontinuation of the drug and if necessary administration of an antihistaminic agent. Anaphylactic shock has rarely been reported. Appropriate resuscitatory measures should be immediately available.
Coagulation disorders can occur usually in a dose related manner including intracranial bleeding, bleeding and/or anaemia due to haemodilution and/or Factor VIII deficiency and acquired von Willebrand's-like syndrome.
Respiratory reactions including non-cardiac pulmonary oedema, bronchospasm and respiratory arrest may also occur.
Cardiovascular reactions including bradycardia, tachycardia, pulmonary oedema and rarely hypotension with subsequent cardiac arrest have also been reported. These are usually mild but can be severe and life threatening. Careful supervision is necessary and appropriate resuscitatory measures should be immediately available.

6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion forms a macro-molecular aggregate with amylase (by which it is degraded) producing a rise in serum amylase levels for up to three days post infusion, which may interfere with blood chemistry determinations, especially with the diagnosis of pancreatitis if determined in this way. This plasma hyperamylase has no pathological significance in the context.

4.9 Overdose

The administration of supratherapeutic doses or infusion at a rate that is too high (greater than 15ml/kg/hr) can bring about an increase of circulating plasma volume which may lead to heart decompensation, pulmonary oedema, and coagulation problems including the prolongation of clotting time.
In the event of an accidental over infusion treatment should be discontinued. The patient should be observed for signs and symptoms of cardiorespiratory decompensation and hepatic and renal functions. Fluid and electrolyte balance should be carefully monitored together with any evidence and bleeding diathesis.
Other symptomatic and supportive measures should be provided as necessary. Hypervolaemia can be treated by administration of a diuretic. If the clinical condition persists then the hetastarch should be restarted at a reduced rate with closer monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code BO5 AA 07: PLASMA SUBSTITUTES AND PLASMA PROTEIN/STARCH FRACTIONS
Hydroxyethyl starches are solutions having long-acting plasma expander activity. It is an artificial colloid derived from a waxy starch composed almost entirely of amylopeptin and has close structural similarity with glycogen. Hydroxyethyl ether groups are introduced into the glucose units and the resultant material is hydrolysed to yield a product with a molecular weight suitable for use as a long-term plasma expander. 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion is characterised by its molar substitution and also by its molecular weight. The average nominal molecular weight is approximately 450,000 daltons. The molar substitution is 0.7, which means that 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion has approximately 7 hydroxyethyl groups for every 10 glucose units of the amylopeptin skeleton. The infusion of 500ml of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion in hypovolaemic patients usually occurs within 30 minutes; after a further 10 minutes an immediate expansion of plasma volume in excess of the volume infused (120% expansion) may be observed, and slowly decreases throughout the succeeding 24-36 hours.

In association with these plasma expansion effects in hypovolaemic states, an effective improvement of the haemodynamics and cardiovascular parameters is observed through an increase in cardiac output, mean arterial pressure and left and right ventricular work index.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydroxyethyl starches are complex, being only slightly dependent on the size of the molecule, but mostly on the degree of molar substitution. Indeed the α-amylase hydrolysis rate and renal excretion is a direct function of the molar substitution, the lower the molar substitution the quicker the body clearance (short plasma and renal half-lives). 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion being characterised by a high molar substitution, is slowly hydrolysed by plasma ∝-amylase leading to a long-term effect of the polymer *in-vivo*. The different molecular weight fractions behave differently; there is a quick elimination of molecules below 50,000 daltons by renal excretion as well as a concomitant partial hydrolysis of the large molecule into molecules of medium molecular weight size.
Molecules within the range of the in-vivo weight average molecular weight are broken down into smaller molecules with time. The plasma concentration of 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion decreases with a $T_{½}$ of approximately 24 hours, ensuring a long-term plasma expansion effect and a prolonged improvement of the haemodynamic properties.
The larger molecules are not removed by dialysis and their elimination is dependent upon:

i) Cellular uptake into body tissues,
ii) back diffusion from tissues into the intravascular space and
iii) enzymatic degradation by α-amylases in the blood, tissues and reticuloendothelial system.

As different size particles are removed from the circulation there is a change of elimination with time. Approximately 30% of the infused 6% w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion is eliminated with a $T_{½}$ of 67 hours, approximately 17% with a $T_{½}$ of 8.5 hours and approximately 18% with $T_{½}$ of 2 hours.

5.3 Preclinical safety data

Modified starches are considered to be practically non toxic meaning that the oral LD_{50} exceeds the stomach volume and is greater than 20g/kg body weight. Two year feeding studies of modified starches at dietary levels up to 30% and at 10% in a three generation test in rats demonstrated “no distinct effect of toxicological significance”. Starch granules have long been known to be absorbed intact into the blood or lymphatic system from the intestinal tract. Hetastarch has been used as a colloidal plasma substitute for several decades.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide
Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

In general it is recommended that other drugs or solutions should not be added to 6%w/v Hetastarch in 0.9% w/v Sodium Chloride Solution for Infusion. When the addition of drugs is required, their safety and compatibility should first be established. It is incompatible with different forms of insulin.

6.3 Shelf Life

The shelf life for the product as packaged for sale in PL-146 containers is 2 years. The shelf life for the product as packaged for sale in PL-2411 containers is 3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The product is enclosed in a plastic bag for solution for infusion. The plastic used to manufacture the container is a Baxter approved plastic, PL-146, and designated “Viaflex®”, or PL-2411, and designated “Viaflex®-E”.

Pack quantities 500 ml x 20.

The PL-146 container is sealed in a plastic overpouch.

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

The plastic container has a outlet port designed for an administration set with a short single connector. If an administrator set with a combined air inlet/fluid path connector has to be used, ensure the air inlet tube is always clamped off.

Instructions for Use

- Remove the protective over pouch (if present) by tearing down the notch and remove the container.
- Carefully straighten hanger and ports, if necessary.
- Squeeze container and inspect for minute leaks and examine solution for visible particles or cloudiness by viewing along seam. Discard unit if leaks, particles or cloudiness are evident.
- Suspend container from base eyelet support.
- Using aseptic techniques the administration set should be prepared.
- The blue protector/twist-off protector covering the outlet port should be removed to allow insertion of the set connector.

- Ensuring that the spike is fully inserted and the roller clamp closed, the set should be primed and administration regulated as required. If the administration set becomes blocked, do not pump contents back into container, but replace equipment.

- Discard all containers and equipment after use whether complete or not. Do not store partly used containers. Do not reconnect partially used bags.

Instructions for Handling

- The PL-146 plastic containers are enclosed within a polyethylene overpouch which is designed to reduce water loss through the plastic.

- They should be stored within their overpouch at a temperature not exceeding 25°C.

- After the overpouch has been removed the container may be stored in this condition for shourt periods of time at 25°C. This should not exceed 30 days.

- The PL-2411 plastic container may be stored at a temperature up to 25°C.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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