

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pentastarch 6% in 0.9% Sodium Chloride Intravenous Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1000 ml of solution contain:

Poly(0-2-hydroxyethyl) starch (Average nominal MW 200,000 Da; molar substitution 0.5)	60.00	g
Sodium Chloride	9.00	g
Osmolarity	308.00	mOsm/L
Colloid Osmotic Pressure	36.00	mmHg
pH	3.50 - 6.50	
Na+	154.00	mmol/L
Cl-	154.00	mmol/L

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Solution for infusion. A clear almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Volume replacement for ( i ) therapy of mild to moderate hypovolaemia and shock in connection with surgery, trauma, infections and burns and ( ii ) acute normovolaemic haemodilution.

The solution is not to be used as a substitute for either blood or plasma.

4.2 Posology and method of administration

Pentastarch 6% is for intravenous use only.

The therapeutic limit is set by the dilution effect. It should be considered that the intravasal volume effect is greater than the infused dose. Careful monitoring of infusion rate and dose prevents circulatory overload The initial 10-20ml should be infused slowly, with the patient under careful observation, in order to detect the occurrence of an anaphylactoid reaction as early as possible.

The daily dose and infusion rate depend upon the patient’s hypovolaemia, age, weight and haemodynamic condition, and should be adjusted accordingly.

In adults the amount usually administered is 500ml to 1000ml. The usual dosage does not usually exceed 1500ml/ day or 20ml per kg bw/day for a typical 70kg bw patient, but in common with other colloids the limiting dose will depend on circulating volume and haematocrit; in patients without cardiovascular or pulmonary risk the solution should only

be used when haematocrit is greater than 30%.

#### Maximum daily dose:

The maximum daily dose is equal to 33ml/kg bw/day or 2500ml /75kg bw/day. For treatments lasting several days, the maximum daily dose must be reduced taking into account dilution effects and haemostasis.

#### Maximum infusion rate:

Do not exceed the maximum administration rate of 20ml/kg bw/hour (or 1500ml/75kg bw/hour)

#### Duration of administration

Administration over several days is indicated only in exceptional cases. Note that the risk of adverse reactions becomes higher as the total dose increases. Clotting parameters must be monitored if Pentastarch 6% is used repeatedly.

#### Recommendations for therapy of hypovolaemia and shock

Unless otherwise prescribed the usual daily volume should be up to 33ml/kg bw/day, or 2500ml /75kg bw/day. The maximum infusion rate should be up to 20ml/kg bw/hour, or 1500ml /75 kg bw/hour. Administration over several days is indicated only in exceptional circumstances.

#### Recommendations for acute normovolaemic haemodilution

Unless otherwise prescribed, it is recommended that prior to surgery donor blood is withdrawn and simultaneously replaced by an infusion of Pentastarch 6% in a ratio of 1:1. The haematocrit should not be lower than 30% after administration. Repeated use is possible if the initial haematocrit is within normal range and is not lower than 30% after therapy. Usually, 2-3x 500ml blood are replaced with 2-3x 500ml Pentastarch 6% at an infusion rate of 1000ml over 15-30 min.

#### Use in children

The safety and efficacy of Pentastarch 6% in children has not been established

#### Use in the elderly

There are no specific dose modifications needed for the elderly.

#### Instructions for Use and Handling

For instructions for the correct administration and use, refer to *section 6.6*

### **4.3 Contraindications**

Pentastarch 6 % is contraindicated in patients with:

- known hypersensitivity to hydroxyethyl starches
- severe congestive heart failure or cardiac decompensation, pulmonary oedema hyperhydration state, or circulatory overload.
- severe coagulation disorders (except for life-threatening emergencies)
- chronic renal failure with oliguria or anuria and patients undergoing haemodialysis

- intracranial bleeding
- hypernatraemia
- hyperchloraemia.
  - constitutional or acquired haemostasis disorders in particular haemophilia and known or suspected von Willebrand's disease.
  - end of pregnancy (labour)

## 4.4 Special warnings and precautions for use

### General Warnings

Infuse the first milliliters of solution slowly in order to detect any hypersensitivity reaction. As with all colloidal substitutes, there is a risk of anaphylactoid reaction whose pathogenic mechanism is unknown up to date, thus the patient should be carefully monitored during the infusion. However, administration of HES in man does not lead to the development of specific antibodies. If any abnormal signs i.e. chills, urticaria, erythema, flush of face or fall in the blood pressure occur during the first minutes of treatment, the infusion must be stopped immediately.

### Precautions for use

Particular attention or dose reduction are mandatory:

- in patients with renal dysfunction, as with any other drug with renal elimination
- in patients at risk of fluid overload
- in patients with known coagulation disorders
- in patients with heart failure or pulmonary oedema

Dehydration states decrease renal tolerance and should therefore be corrected before use of Pentastarch 6 %. Adequate fluid intake must be ensured; serum electrolytes and renal function must be monitored during therapy.

Regular monitoring of haemostasis by measuring APTT and possibly factor VIIIc in order to detect von Willebrand's disease is recommended, especially when Pentastarch 6% is administered in high dosage or on subsequent days. Iterative and prolonged administrations lead to a risk of accumulation of HES in liver, especially in cells of the macrophage system (Kupfer cells). Accumulation of HES may be accompanied by poor general condition, impaired liver function and/or the onset or worsening of portal hypertension.. This effect is particularly serious in patients with chronic liver disease. Safety of use, in particular concerning the risk of accumulation of the substance has not been established beyond 8 days of administration. The long term effects of storage of Pentastarch 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

Incompatibilities may occur when mixing with other drugs. It is generally recommended to refrain from adding other drugs or solutions to Pentastarch 6 % . Use in conjunction with heparin or oral anticoagulants may extend clotting time. When this solution is administered as an emergency in patients whose blood group is not known, the sample to be used for grouping as well as for detection of irregular agglutins must be drawn first (risk of false positives). The product is not compatible with different forms of insulin. Special care should be exercised with patients currently taking concomitant medication, in particular  $\beta$ -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 borne in mind. The nephrotoxicity of aminoglycoside antibiotics may be increased when co-administered with the product. There is no experience concerning any possible interaction with nutritional products.

## 4.6 Pregnancy and lactation

There are no adequate data from the use of Pentastarch 6% in pregnant women. No reproduction studies in animals have been carried out with this solution, but studies with similar hydroxyethylstarch products have revealed evidence of vaginal bleeding and embryocidal effects after repeated use in animals. There is also an increased risk of anaphylactic

reaction with subsequent fetal brain damage. Pentastarch 6% should not be given to pregnant women or during labour with epidural anaesthesia, because of the risk of death or serious neurologic sequelae concerning the child. Breast feeding should be stopped as it is not known whether Pentastarch 6% is excreted into human milk.

#### 4.7 Effects on ability to drive and use machines

Not applicable.

#### 4.8 Undesirable effects

Pentastarch 6 % forms a macro-molecular aggregate with amylase (by which it is degraded) producing a rise in serum amylase levels for up to three days after infusion. This may affect blood count results and therefore especially interfere with the diagnosis of pancreatitis based on these results. This hyperamylasaemia is without pathological relevance.

The following undesirable effects have been reported:

Anaphylactoid reactions, ranging from simple skin rash to the development of circulatory disorders, shock, bronchospasm and respiratory and/or cardiac arrest. Rare cases of itching have been reported. If an intolerance reaction occurs, the infusion must be stopped immediately and appropriate treatment administered.

Respiratory reactions, including non-cardiac pulmonary oedema, bronchospasm and respiratory arrest may also occur. These are usually mild but can be severe and life threatening. Careful supervision is necessary and appropriate resuscitatory measures should be available immediately.

Haemostasis disorders of von Willebrand's disease reflected by prolongation of APTT and bleeding time and decreased VIIIc/vWF complex levels, have been observed with other hydroxylethylstarches with the same molecular weight, particularly when Pentastarch 6% is administered in higher dosage on subsequent days.

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 available immediately.

Impaired liver function (initially taking the form of poor general condition) and/or the onset or worsening of portal hypertension have been reported during prolonged and iterative use with hydroxylethylstarches with the same molecular weight but more substituted.

Miscellaneous reactions Other reactions such as chills, paraesthesia, headache, weakness, vomiting, skin rashes, submaxillary and parotid gland enlargement, muscle pains and peripheral oedema of the lower extremities have been reported. Mild dermatological reactions consisting of persistent and reversible itching (pruritus) have been reported. If such reactions occur they are readily controlled by discontinuation of the drug and if necessary administration of an antihistaminic agent.

#### 4.9 Overdose

In the event of accidental over infusion administration must be discontinued. Hypervolaemia may be treated by administration of a diuretic.

The patient must be observed for signs and symptoms of cardio respiratory decompensation, and hepatic as well as renal functions need to be monitored. Fluid and electrolyte balance as well as coagulation parameters should be carefully monitored.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Plasma Substitutes and Plasma protein/starch fractions

**ATC Code:** BO5 AA 07

Pentastarch 6% is an isotonic solution consisting of 6% of a low substituted hydroxyethylstarch. The mean molecular weight is 200,000D. The structure of the parent substance, amylopectin, is close to that of glycogen. Binding of hydroxyethyl radicals delays the hydrolysis of amylopectin by plasma or amylases and defines its degree of substitution or molar substitution rate, which is the hydroxyethyl/glucose molar ratio (0.43-0.55). The degree of blood volume expansion depends upon the mean molecular weight in number and molar substitution rate. Hydrolysis of hydroxyethylstarch polymers gradually releases substances which have an oncotic potential in their turn before being eliminated. The administration of 500ml of this solution in 30 minutes to non hypovolaemic subjects results in blood volume expansion (in relation to the volume infused): 133% at 15minutes; 104% at 3 hours (iso-oncotic effect).

Infusion of Pentastarch 6% in hypovolaemic situations restores blood mass and improves:

- haemodynamic parameters (blood pressure, right and left filling pressure)
- cardiac and rheologic parameters (cardiac output and work, systolic ejection index)
- hourly urine output

In all cases, in the absence of previous renal failure, maintenance of an effective blood volume preserves renal function with maintenance of urine output, increased natiuresis and preservation of endogenous creatinine clearance.

### 5.2 Pharmacokinetic properties

Hydroxyethylstarch undergoes enzyme breakdown by two alpha amylases, all the more difficult as the molar substitution rate is great, and which leads to the formation of oligosaccharides and polysaccharides of various molecular weights. Breakdown to glucose is slight, initially and transitory. Elimination half-life is about 3-5 hours. Breakdown products are eliminated via the kidney: 50% of the dose administered is found in the urine in less than 24 hours.

### 5.3 Preclinical safety data

No toxicity studies with Pentastarch 6% have been carried out. Studies in normovolaemic animals with other hydroxyethylstarches have failed to reach a toxic dose, the limiting factor being the amount of fluid administered. In subchronic toxicity studies, administration of a dose of up to 4.0g/kg bw, close to the therapeutic dose, has been found to be associated with:

- significant and dose-dependent lengthening of the prothrombin time,
- a dose-dependent fall in haemoglobin, haematocrit and red cell levels,
- increased weight of the kidneys, liver and heart, and
- vacuolization of RES cells of various organs.

These changes are reversible 15 days after administration is stopped, except for vacuolization of liver cells.

Animal studies have also revealed embryotoxic and teratogenic effects following repeated and hypervolaemic injections, probably as a consequence of circulatory overload.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium hydroxide and hydrochloric acid (for pH adjustment), water for injections.

### 6.2 Incompatibilities

Since the compatibility of additives has not been established with either the Pentastarch solution for infusion or the container, the addition of other medicinal products should not occur.

### 6.3 Shelf Life

2 years (250 ml) and 3 years (500 ml).

### 6.4 Special precautions for storage

There are no specific storage requirements.

### 6.5 Nature and contents of container

250 ml x 30 units or 500 ml x 20 units in Viaflex-E (polyolefine) bag.

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

1. Check for minute leaks by squeezing the bag firmly. Examine solution for visible particles or cloudiness by viewing along seam. Discard unit if leaks, particles or cloudiness are evident. Only use if the solution is clear and the container is undamaged.
2. Suspend container from base eyelet support.
3. Prepare administration set using aseptic techniques.
4. Remove twist-off protector covering the outlet port to allow insertion of the set connector.
5. ensure that the spike is fully inserted and the roller clamp closed, then prime set and adjust administration rate as desired. If the administration set is blocked, do not squeeze contents back into container, but replace set.
6. Discard all containers and equipment after use – irrespective of the filling level. Do not store partly used containers.
7. Do not reconnect partially used bags.

## 7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.,  
Caxton Way,  
Thetford,  
Norfolk IP24 3SE,  
United Kingdom.

## 8 MARKETING AUTHORISATION NUMBER

PA 0167/110/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 05 April 2002