Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

HyperHAES
Soution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml solution for infusion contain:

Poly(O-20hydroxyethyl) starch (Molar substitution 0.43-0.55) (Mean molecular weight 200,000 Da)	60.0 g
Sodium chloride	72.0 g
Na^+	1232 mmol/l
Cl^-	1232 mmol/l
Theoretical osmolarity	2464 mosml/l
pH	3.5 – 6.0
Titratable acidity	< 1.0 mmol NaoH/l

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
A clear to slightly opalescent solution, colourless to slightly yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Initial**,** single dose treatment of acute hypovolaemia and shock (“small volume resuscitation”)

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

4.2 Posology and method of administration

Maximum dose:
HyperHAES is to be administered as a single intravenous bolus dose (approximately 4 ml/kg bodyweight = 250 ml for a patient with a body weight of 60-70 kg).

Mode of administration:
HyperHAES should be given as a single intravenous bolus dose or pressure-infusion (a full dose within two to five minutes).

Although the osmolarity of HyperHAES is very high, the product can be administered via peripheral venous route. If available, central venous route is preferred, but not mandatory.

Duration of treatment:
HyperHAES is intended for *single* administration only. Repeated infusions are not recommended.

Treatment with HyperHAES should be immediately followed by a standard volume therapy (e.g. electrolytes and colloids), dosed adequately to the needs of the patient.

In case of subsequent standard volume therapy with products containing hydroxyethyl starch the initial dose of 15 g HES 200/0.5 administered with HyperHAES should be included in the total cumulative dose.

As with all other artificial colloids there is a risk of anaphylactic reactions. Patients must be monitored carefully and treatment discontinued if any signs or symptoms occur.

Use in children
The safety and efficacy of HyperHAES in children has not been established.

Use in elderly
There are no specific dose modifications needed for the elderly.

Instruction for Use and Handling
For the correct administration and to avoid the risk of air embolism, refer to *section 6.6.*

4.3 Contraindications

If any one or more of the following clinical conditions apply, HyperHAES should not be used in acute and life-threatening conditions or only after careful benefit/risk evaluation:

- Known hypersensitivity to hydroxyethyl starches
- Circulatory overload
- Decompensated congestive heart failure
- Severe liver insufficiency
- Known haemostasis disorders
- Renal failure with anuria
- End of pregnancy (labour), *see section 4.6.*
- Hyperosmolarity
- Dehydration
- Severe hypernatremia or hyponatremia
- Severe hyperchloremia or hypochloremia.

4.4 Special warnings and precautions for use

Attention should be paid to increased serum osmolarity**,** especially in diabetes patients.

Serum electrolytes, serum osmolarity and fluid balance should be monitored regularly.

Attention should be paid to the possibility of increased haemorrhage caused by aggressive fluid resuscitation (leading to increased perfusion pressures) and haemodilution effects of HyperHAES.

The patient should be carefully monitored during the infusion. As with all colloidal volume substitutes, there is a risk of anaphylactoid reaction whose pathogenetic mechanism is unknown up to date. However, administration of HES in man usually does not lead to the development of specific antibodies.

Blood pressure and possibly haemodynamic monitoring is required in order to avoid any risk of vascular overload.

If any abnormal signs, i.e. chills, urticaria, erythema, flush of face, or fall of the blood pressure, occur during the first minutes of treatment, the infusion must be stopped immediately.

If administered in conditions without marked hypovolaemic shock, vasodilatative symptoms (transient hypotension) or symptoms of volume overload (left heart failure, arrhythmias, pulmonary hypertension) may occur, especially in situations where cardiac function and coronary blood flow are limited (e.g. cardiac surgery).

4.5 Interaction with other medicinal products and other forms of interaction

Use in conjuction with heparin may extend bleeding time.

Please refer to *section 4.8 "Undesirable effects"* concerning the concentration of serum amylase which can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

4.6 Pregnancy and lactation

There are no clinical experiences with HyperHAES during pregnancy.

The product should not be administered to pregnant women during labour to prevent hypotension induced by epidural anaesthesia, as there is a risk of a maternal anaphylactic or anaphylactoid reaction.

Breast feeding:
It is not known whether hydroxyethyl starch is excreted into human milk, but in view of the low hydroxyethyl starch dose administered with this product there is considered to be no risk.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following undesirable effects have been reported with infusion solutions containing hydroxyethyl starch:

Anaphylactoid reactions, ranging from simple skin rash to the development of circulatory disorders, shock, bronchospasm and cardiac arrest (in rare cases). In the event of an intolerance reaction, the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated.

Respiratory reactions, although usually mild, can be severe and life- threatening if non-cardiac pulmonary oedema, bronchospasm and respiratory arrest occur. Careful supervision is necessary and appropriate resuscitatory measures should be available immediately.

Cardiovascular reactions, including bradycardia and tachycardia are usually mild but can be severe and life-threatening, if pulmonary oedema and rarely hypotension with subsequent cardiac arrest occur. Careful supervision is necessary and appropriate resuscitatory measures should be available immediately.

If hypertonic solutions are administered in conditions without marked hypovolaemic shock, vasodilatative symptoms (transient hypotension) may occur commonly.

Undesirable effects of hypertonic solutions, like central pontine myelinolysis, cerebral bleeding (rupture of meningeal connecting veins) caused by dehydration and shrinking of tissue respectively, and local intolerance reactions (thrombophlebitis, phlebothrombosis after peripheral administration) are considered possible.

The concentration of serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

With the administration of hydroxyethyl starches disturbances of blood coagulation can occur depending on the dosage.

Table: Frequency of Occurrence of Adverse Drug Reactions

System Organ Class	Adverse Drug Reaction	Frequency of Occurrence
Vascular disorders	Hypotension in patients without marked hypovolaemic shock	Common (>=1% - <10%)
Cardiac disorders	Left heart cardiac failure in patients without marked hypovolaemic shock	Common (>=1% - <10%)
	Arrhythmia in patients without marked hypovolaemic shock	Common (>=1% - <10%)
	Pulmonary hypertension in patients without marked hypovolaemic shock	Common (>=1% - <10%)
Investigations	Increase of serum amylase	Common (>=1% - <10%)
Immune system disorders	Anaphylactoid reactions	Rare (>0.01% - =<0.1%)
Metabolism and nutrition disorders	Hypernatremia	Very common (>10%)
	Hyperchloremia	Very common (>10%)
	Dehydration	Not observed yet, but considered possible
Blood and lymphatic system disorders	Coagulation disorders	Not observed yet, but considered possible
Nervous system disorders	Central pontine myelinolysis	Not observed yet, but considered possible
Respiratory, thoracic and mediastinal disorders	Respiratory reactions	Not observed yet, but considered possible
General disorders and administration site conditions	Local intolerance reactions	Not observed yet, but considered possible

4.9 Overdose

Overdosage may cause hypernatremia. In this case, fluid compensation, and induction of forced diuresis in hypervolaemic conditions have to be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: B05AA07

HyperHAES is a hypertonic iso-oncotic solution of 7.2% sodium chloride and 6% hydroxyethyl starch. Due to the high osmolarity of HyperHAES (2464 mosm/l) fluid, primarily from the interstitial compartment, is rapidly shifted into the vascular compartment. Haemodynamic parameters like blood pressure and cardiac output are rapidly increasing depending on the dosage and infusion rate. Low haemodynamic values are returning to normal. The increase of intravascular volume lasts only for a short time and has to be stabilised by immediate administration of an adequate standard volume therapy (e.g. electrolytes and colloids) after infusion of HyperHAES.

5.2 Pharmacokinetic properties

Hydroxyethyl starch undergoes enzymatic breakdown by alpha amylases which leads to the formation of oligosaccharides and polysaccharides of various molecular weights.

Hydroxyethyl starch (HES 200/0.5) has a plasma half-life of approximately 4 hours. Hydroxyethyl starch is mainly eliminated renally; 50% of the dose administered is found in the urine in less than 24 hours. Small amounts are temporarily stored in the tissues. Hydroxyethyl starch (HES 200/0.5) can be eliminated by diafiltration, but not by dialysis. The intravascular half-life and retention time, respectively, are correlating with the severity of renal insufficiency.

After 30 minutes, sodium chloride is distributed over the whole extracellular space. Sodium chloride is mainly eliminated renally, small amounts are excreted transcutaneously.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproduction toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Hydroxhloric acid
Water for injections

6.2 Incompatibilities

This pharceutical product should not be mixed with other products while compatibility data are not available.

6.3 Shelf Life

36 months
This product should be used immediately after opening.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Polyolefine bag (freeflex) with overwrap:	1 x 250 ml 10 x 250 ml 20 x250 ml 30 x 250 ml 35 x 250 ml 40 x 250 ml

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

To be used immediately after the bag is opened.

To avoid the risk of air embolism, the air msut be removed from both the bag and infusion system prior to administration via pressure infusion.

Any unused solution should be discarded.

Use only clear to slightly opalescent solution, colourless to slightly yellow-solutions and undamaged containers.

Do not reconnect partially used bags.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Ltd.
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8 MARKETING AUTHORISATION NUMBER

PA 0566/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17 May 2005

10 DATE OF REVISION OF THE TEXT

March 2008