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 Vitafusal.

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 various intensities may occur after administration of hydroxyethyl starch. All patients receiving starch infusions should therefore be closely monitored for anaphylactic reactions. 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.

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

Vitafusal 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.

Vitafusal is iso-oncotic, i.e. the intravasal volume increase is equivalent to the infused volume.
As its electrolyte component, Vitafusal contains Ringer's acetate solution with an iso-ionic cation composition and with acetate as a metabolisable anion. Acetate is oxidised and has an alkalising effect in the acid-base balance. Owing to the proportion of metabolizable anions, an additional partial indication is existing in patients to have a tendency to metabolic acidosis. The specific composition of Vitafusal combines the beneficial properties of Ringer's acetate solution (balanced acid-base component) with the effective volume efficacy of colloid HES 130/0.42.

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 Vitafusal may reduce haematocrit and plasma viscosity.

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

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 Vitafusal, plasma clearance is 19 ml/min and the AUC is 58 mg x h/ml. The terminal half-life is about 12 hours.

5.3 Preclinical safety data
Vitafusal 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 ASAT and ALAT. 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 36%

6.2 Incompatibilities
Incompatibilities can occur when Vitafusal is mixed with other medications, especially solutions containing phosphate or carbonate.

6.3 Shelf life

Glass bottle:	3 years
Bag (Sengewald):	3 years
Bag (PolyCine):	18 months
Polypropylene bottle:	18 months

6.4 Special precautions for storage
Do not freeze.

6.5 Nature and content of container
Vitafusal is available in the following packaging and pack sizes:

Type II glass bottle with butyl rubber stopper
10 x 500 ml

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

Polypropylene bottle with butyl rubber stopper
10 x 500 ml

6.6 Instructions for use and handling and disposal
Use immediately after first opening.
Use bag unvented.
Any unused solution should be discarded.
Use only clear solutions from intact containers.

7 Pharmaceutical Authorisation Holder

Serumwerk Bernburg AG
Hallesche Landstraße 105 b
06406 Bernburg
Germany

8 Marketing Authorisation Number

60252.00.00

9 Date of First Authorisation/Renewal of Authorisation

02 November 2004

10 Date of Revision of the Text

November 2005