The use of Voluven in critically ill patients, including those with severe sepsis, is associated with an increased risk of death or the need for renal replacement therapy.

1 PRODUCT NAME

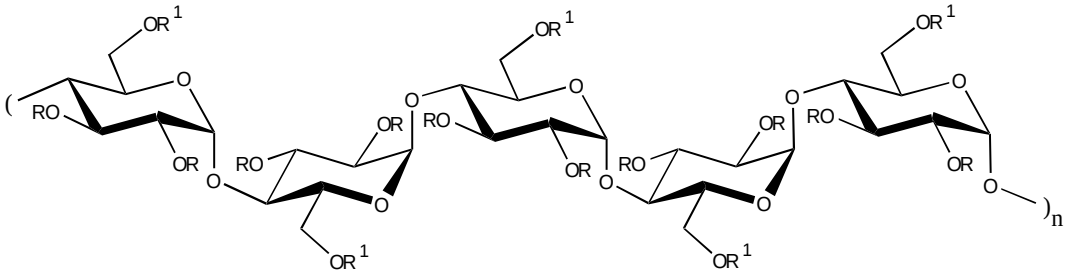
VOLUVEN® 6% solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active	Amount (L)
Hydroxyethyl Starch 130/0.4	60g
Excipient	
NaCl (Na^+ 154 mmol, Cl^- 154 mmol)	9g

For the full list of excipients, see Section 6.1 List of excipients.

Chemical structure



R = -H, $-CH_2CH_2OH$
R^1 = -H, $-CH_2CH_2OH$ or glucose units

Molar substitution 0.38 – 0.45

Average Molecular weight: 110,000 - 150,000 Dalton

Mean molecular weight (Mw) 130,000

Chemical name: Poly (O-2 hydroxyethyl) starch

Active Substance	**CAS number**
Hydroxyethyl Starch 130/0.4	9005-27-0

Hydroxyethyl Starch 130/0.4 is a white to yellowish white, odourless and tasteless, amorphous powder, readily soluble in water at room temperature, soluble in DMSO, practically insoluble in most organic solvents.

3 PHARMACEUTICAL FORM

Solution for infusion.
Voluven 6% isotonic solution is colourless and clear and is slightly acidic (pH 4.0-5.5).
Osmolality approx 304 mOsm/kg water
Theoretical osmolarity 308 mosm/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. The use of Voluven is not a substitute for the appropriate use of packed red blood cells or fresh frozen plasma.

4.2 Dose and method of administration

For intravenous infusion.

Use of Voluven should be restricted to the initial phase of volume resuscitation with a maximum duration of use of 24 hours.

Administration of Voluven may cause anaphylactic reactions that may manifest as acute hypotension. In all patients, the initial 10-20 mL of Voluven should be infused slowly, keeping the patient under close observation for anaphylactic/anaphylactoid reactions manifesting as unexpected hypotension, or the development of wheeze or rash, (Please also refer to section 4.4 and 4.8).

The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect).

In clinical trials, infusions up to 33 mL/kg/day were most commonly used. There is limited experience with infusions between 33 mL/kg/day and 50 mL/kg/day.

Hepatic and renal monitoring is necessary at higher doses,(Please also refer to section 4.4).

Paediatric population

Data are limited in children. It is therefore recommended not to use HES products in paediatric patients, (Please also refer to section 4.4).

Instructions for use/handling

Each container should be used in one patient and on one occasion only. It should be used immediately after the bottle or bag is opened and any unused solution must be discarded. The solution contains no antimicrobial preservatives. Do not use if the solution is not clear or if the container is damaged.

(Please also refer to ***Appendix "SPECIAL HANDLING INSTRUCTIONS")***.

4.3 Contraindications

Voluven should not be used, if any one or more of the following clinical conditions apply:

- Critically ill patients (typically admitted to intensive care unit), including those with sepsis
- Fluid overload (hyperhydration), especially in cases of pulmonary oedema and congestive cardiac failure
- Patients with pre-existing coagulation or bleeding disorders
- Renal failure with oliguria or anuria not related to hypovolaemia
- Patients receiving dialysis treatment
- Intracranial bleeding
- Severe hypernatraemia or severe hyperchloraemia
- Known hypersensitivity to hydroxyethyl starches
- Patients with severe liver disease

4.4 Special warnings and precautions for use

Voluven is not a substitute for red blood cells or coagulation factors in plasma.

Fluid Overload

Administration of Voluven may cause fluid overload, resulting in cardiac and pulmonary failure. Administration should be carefully titrated to relevant physiological endpoints. Particular care must be taken in patients with cardiac insufficiency or severe renal dysfunction.

Dehydration

Intravenous fluid resuscitation in cases of severe dehydration should be through the use of crystalloid solutions.

Bleeding risk

Voluven administration may cause coagulopathy, either through a direct effect; or indirectly through the dilution effect. This will increase the risk of bleeding. Administration should be ceased if a coagulopathy develops or excessive bleeding occurs.

Cardiopulmonary bypass

Coagulation status must be closely monitored during cardiopulmonary bypass in patients receiving Voluven because of the bleeding risk.

Surgery and trauma

There is a lack of robust, long-term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long-term safety. Other available treatment options should be considered.

Renal function

It is important to supply sufficient fluid and to regularly monitor kidney function and fluid balance. Avoid use in patients with pre-existing renal dysfunction.

Serum electrolytes should be monitored.

Discontinue use of HES at the first sign of renal injury. A need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in any case of deterioration of renal function.

Liver function

Monitor liver function in patients receiving HES products, including Voluven 6%.

Anaphylactic/anaphylactoid reactions

Regarding the occurrence of anaphylactic/anaphylactoid reactions please refer to" " section 4.8 UNDESIRABLE EFFECTS".

Laboratory Assessments

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, serum electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

Use in the elderly
Clinical experience (including published trials) has included elderly populations, some exclusively with patients of 70 years and above. Dose reduction was not required and safety has been comparable to control treatments (gelatin or albumin) in elderly patients.

Paediatric use
There is lack of robust, long-term safety data in children undergoing surgical procedures. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long-term safety and informed consent obtained from the patient/parent where possible. Other available treatment options should be considered.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interactions
No interactions with other drugs or nutritional products are known to date.

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 Fertility, pregnancy and lactation
Effects on fertility
HES 130/0.4 10% solution in 0.9% sodium chloride did not impair fertility in male rats at IV doses up to 5 g/kg/day. In female rats, no adverse effects on fertility were observed at doses up to 2.5 g/kg/day. Slight inhibition of ovulation, evident as a decrease in corpora lutea and resulting in a reduced number of fetuses, was observed at a maternotoxic dose of 5 g/kg/day IV.

Use in pregnancy (Category B3)
No clinical data are currently available on the use of Voluven during pregnancy. Studies in pregnant rats and rabbits showed that the type of hydroxyethyl starch present in Voluven was associated with embryofoetal toxicity following IV administration at 5 g/kg/day. The embryofoetal toxicity included resorption, stillbirths, reduced foetal weight and delayed foetal development.

Voluven should not be used during pregnancy, unless the expected therapeutic benefit clearly outweighs the potential risk to the foetus.

Use in lactation
There are currently no clinical data on the use of Voluven in breast-feeding women. A study in lactating rats showed that the type of hydroxyethyl starch present in Voluven was associated with decreased postnatal growth and development following IV administration at 5 g/kg/day. It is not known whether the hydroxyethyl starch is excreted into human milk. As many drugs are excreted into human milk, Voluven should not be used in breast-feeding women.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Medicinal products containing hydroxyethyl starch may rarely lead to anaphylactic/anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema). In the event of an intolerance reaction occurring, the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated.

Prolonged administration of high doses of hydroxyethyl starch commonly causes pruritus (itching) which is a known undesirable effect of hydroxyethyl starches.

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

At high dosages the dilution effects may result commonly in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and a decrease in haematocrit.

With the administration of Voluven disturbances of blood coagulation beyond dilution effects can occur rarely depending on the dosage.

TABLE: FREQUENCY OF OCCURRENCE OF ADVERSE DRUG REACTIONS

System Organ Class	**Adverse Drug Reaction**	**Frequency of Occurrence**
Blood and lymphatic system disorders	Coagulation disorders beyond dilution effects	***Rare*** ***(*****in high doses*****)*** (≥0.01% to <0.1%)
Immune system disorders	Anaphylactic/ Anaphylactoid reactions	Rare (≥0.01% to <0.1%)
Skin and subcutaneous tissue disorders	Pruritus	***Common*** ***(*****dose dependent*****)*** ***(≥1% to < 10%)***
Investigations	Increase of serum amylase	***Common*** ***(*****dose dependent*****)*** ***(≥1% to < 10%)***
	Decrease of haematocrit	***Common*** ***(*****dose dependent*****)*** ***(≥1% to < 10%)***
	Decrease of plasma proteins	***Common*** ***(*****dose dependent*****)*** ***(≥1% to < 10%)***

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Excessive or rapid administration of volume expanders such as Voluven may result in fluid overload with resulting cardiac and pulmonary failure. If this occurs, volume replacement should be ceased and supportive care provided. Use of diuretics may be required.

For advice on the management of overdose, contact the national Poison Information Centre on 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions.
ATC code: B05A A07

5.1 Pharmacodynamic properties

Mechanism of action

Voluven is an artificial colloid for volume replacement whose effect in intravascular volume expansion and haemodilution depends on the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130,000 Da), the concentration (6%), the degree of substitution (C_2/C_6 ratio) of approx. 9:1 as well as the dosage and infusion rate.

Infusion of 500 mL Voluven in 30 minutes in volunteers results in a plateau-like non-expansive volume increase of approximately 100% of the infused volume which lasts for approximately 4 to 6 hours.

Isovolaemic exchange of blood with Voluven maintains blood volume for at least 6 hours.

Clinical trials

In 21 randomised controlled clinical trials a total of 1315 subjects have been studied; 768 receiving Voluven and 547 receiving another colloid or crystalloid solution. These trials have been conducted in order to evaluate the efficacy and safety of Voluven. Adult and paediatric surgical patients and ICU patients treated for volume replacement make up 705 subjects (355 receiving Voluven).

The patient population of the primary efficacy clinical studies (clinical settings of volume replacement therapy) included various types of surgery (orthopaedic, urologic, cardiac, paediatric and aortic surgery), trauma, intensive care, situations in which hypovolaemia is treated (pre-, intra-, and postoperative) or prevented (autologous blood donation, acute normovolaemic haemodilution). The comparators for these controlled studies were HES 200/0.5, HES 450/0.7 (hetastarch), gelatin, human serum albumin and crystalloids.

197 patients received infusions from 30 to > 50 mL/kg of Voluven. This dose range is supported by experience in the published literature.

Analysis of coagulation parameters revealed significant differences between Voluven and HES 200/0.5: significantly higher levels of von Willebrand factor, Factor VIII, and Ristocetin cofactor with Voluven compared to HES 200/0.5. Furthermore, there were reduced blood loss and transfusion requirements in the Voluven-treated patients compared to the HES 200/0.5 treated patients.

Clinical trials demonstrated comparable efficacy of Voluven with the control colloids to maintain or restore haemodynamics as shown by comparable volume of colloid administration (primary efficacy endpoint) and similar stabilisation of haemodynamics (secondary endpoints). There was no difference in mortality between groups. Regarding safety, Voluven proved to be at least as safe as the comparators.

Published clinical trials conducted in elderly populations have included two studies in which 90 elderly patients (age range 70 to 86 years) were studied. In both trials, the analysed kidney function did not differ between Voluven and gelatin or human albumin. No specific dosage adjustments were required in these elderly patients.

Of the total number of patients in clinical trials of Voluven (n=471), 25% were 65 to 75 years old, while 7% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects

and younger subjects. Other reported experience has not identified specific risks for the application of Voluven in this patient group.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydroxyethyl starch is complex and depends on the molecular weight and mainly on the molar substitution degree. When applied intravenously, molecules smaller than the renal threshold (60,000-70,000 Da) are readily excreted in the urine while larger ones are metabolised by plasma α-amylase before the degradation products are renally excreted.

The mean in vivo molecular weight of Voluven in the plasma is 70,000-80,000 Da immediately after infusion and remains above the renal threshold throughout the therapeutic period.

The volume of distribution is about 5.9 litres. Within 30 minutes of infusion the plasma level of Voluven is still 75% of the maximum concentration. After 6 hours the plasma level has decreased to 14%. Following a single dose of 500 mL hydroxyethyl starch plasma levels almost return to baseline after 24 hours.

Plasma clearance was 31.4 mL/min when 500 mL of Voluven was administered, with an AUC of 14.3 mg/mLxh, which shows non-linear pharmacokinetics. Plasma half-lives were $t_{½\alpha}$=1.4h and $t_{½\beta}$=12.1h when 500 mL were administered on a single occasion.

Using the same dose of 500 mL in subjects with stable mild to severe renal impairment, the AUC moderately increased by a factor of 1.7 (95% confidence limits 1.44 and 2.07) in subjects with ClCr < 50 ml/min compared to > 50 ml/min. Terminal half life and peak HES concentration were not affected by renal impairment. At ClCr ≥ 30 ml/min, 59% of the drug could be retrieved in the urine, vs 51 % at ClCr 15 to 30 ml/min. Plasma levels of Voluven returned to baseline levels 24 hours following infusion.

No significant plasma accumulation occurred even after a daily administration of 500 mL of a 10% solution to volunteers containing HES 130/0.4 over a period of 10 days. In an experimental model in rats using repetitive doses of 0.7 g/kg BW per day of Voluven over 18 days, 52 days after the last administration tissue storage was 0.6% of the total administered dose.

Hydroxyethyl starch (HES) is a derivative of amylopectin, which is a highly branched compound of starch. In humans and animals amylopectin is rapidly hydrolysed by amylase. In order to reduce the metabolic degradation, glucose residues of the amylopectin are reacted with ethylene oxide. The hydroxyethyl groups can be introduced at three positions (C_2,C_3,C_6) of the glucose residues. The degree of substitution and the substitution pattern expressed by the C_2/C_6 ratio determines the enzymatic degradation of HES. Voluven is characterised by its molar substitution, by its molecular weight and the C_2/C_6 ratio.

Molecular weight (Mw): The molecular weight indicates the weight average and it is between 110,000 and 150,000 Dalton, which corresponds approximately to 609 to 830 partially hydroxyethylated glucose units.

Molar substitution (MS): The ratio of hydroxyethyl groups to glucose units is called the molar substitution (MS). The MS for this substance is 0.4 (range 0.38 – 0.45) and determines the molar ratio of hydroxyethyl ether groups to glucose units.

C_2/C_6 ratio: This parameter gives information about the preferred position of hydroxyethylation and reflects the different intrinsic reactivity of the secondary and the primary alcohol functionality at the respective positions of the glucose ring. The value of the C_2/C_6 ratio should be higher than 8.

5.3 Preclinical safety data

Genotoxicity

In vitro genotoxicity studies revealed no evidence for mutagenicity or clastogenicity for the type of hydroxyethyl starch present in Voluven. An in vivo chromosomal aberration study in rats was also negative at the tested dose of 5 g/kg/day IV.

Carcinogenicity

The carcinogenic potential of Voluven has not been investigated in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients	Amount
Sodium chloride	9g/L
Sodium hydroxide to adjust pH	q.s
Hydrochloric acid to adjust pH	q.s
Water for injection	q.s

6.2 Incompatibilities

The mixing with other drugs should be avoided.

6.3 Shelf life

Approved shelf life as packaged for sale:

Freeflex bag	36 months
Plastic PE bottle	36 months
Glass bottle	60 months

The product should be used immediately after opening.
For single use only. Discard unused portion.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Each container should be used in one patient and on one occasion only. It should be used immediately after the bottle or bag is opened and any unused solution must be discarded. The solution contains no antimicrobial preservatives. Do not use if the solution is not clear or if the container is damaged.

6.5 Nature and contents of container

Colourless type II glass bottle with halobutyl rubber closure and aluminium cap	10 x 250 ml; 10 x 500 ml
Polyolefin bag (Freeflex®) with overwrap	10, 20, 30, 35, 40 x 250 ml 10, 15, 20 x 500 ml
Plastic Polyethylene PE (bottlepack)	10 x 500ml

All packaging components for the Freeflex® bag are latex- and PVC-free.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed in accordance with local requirement.

7 MEDICINE SCHEDULE
General Sale Medicine

8 SPONSOR
Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Mangere, Auckland 2022
New Zealand
Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
2 May 2002

10 DATE OF REVISION OF TEXT
08 April 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformat Datasheet as per new Medsafe datasheet form
3	Added Theoretical osmolarity 308 mosm/l
6.3	Added Shelf life data
6.4	Duplicated statement from section 4.2 “dose and method of administration”concerning storage after opening.
6.5	Added *Freeflex* Bags and bottle description and also included pack size not marketed
8	New Zealand sponsor address changed

APPENDIX: SPECIAL HANDLING INSTRUCTIONS

Method of administration

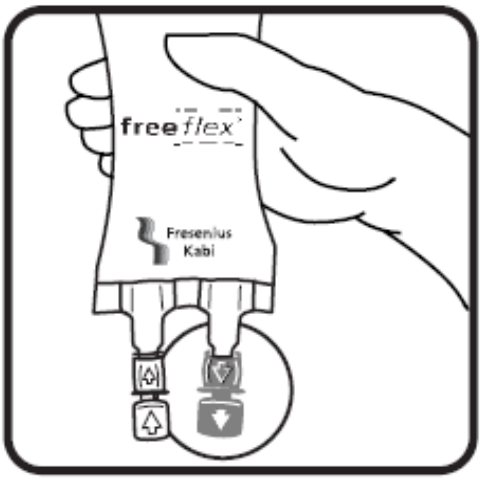
Precautions to be taken before administering product.

Before administering the product in plastic bags to the patient, review these directions:

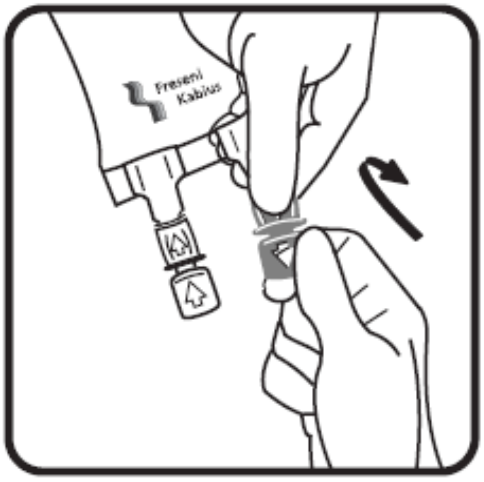
freeflex® IV Solution Container

(1) Check the expiry date and the solution for visible particles or cloudiness, do not use unless the solution is clear. Inspect the container for damage or leakage, if damaged do not use.

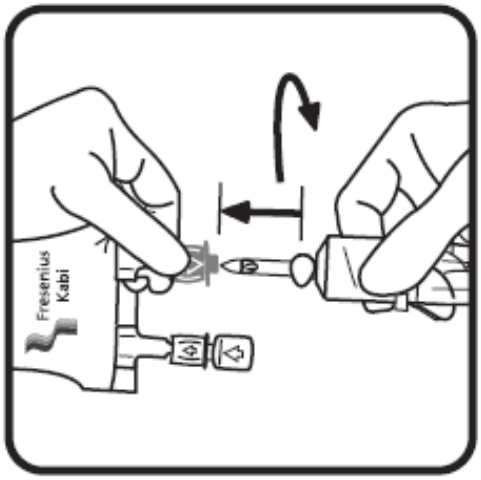
(2) Using the pre-cut corner tabs, peel open and remove the over-wrap.



(3) Identify the blue infusion (administration) port. **Use the BLUE port only to administer solution**. Never use the white port.



(4) Break off the blue tamper-evident cover from the freeflex® blue infusion port.



(5) Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike. Use a non-vented standard infusion set and close air inlet. Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

Warnings

1. Do not remove the freeflex® IV container from its overwrap until immediately before use.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
3. Do not administer unless the solution is clear, free from particles and the freeflex® IV container is undamaged.
4. Voluven should be used immediately after insertion of the administration set.
5. Use the BLUE port only to administer solution. Never use the white port.
6. Do not vent.
7. If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.
8. Discontinue the infusion if an adverse reaction occurs.
9. It is recommended that administration sets are changed at least once every 24 hours.
10. For single use only. Discard unused portion.