

PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Green-VIII-JAKEL 250 IU Powder and Solvent for Solution for Infusion

2. QUANTITATIVE COMPOSITION

Each 1 vial contains nominally 250 IU human coagulation factor VIII, as detailed below:

Component	Quantity per vial
Human Blood Coagulation Factor VIII	250 IU
Sodium Citrate (stabilizer)	29.4 mg
Calcium Chloride (stabilizer)	1.5 mg
Glycine (stabilizer)	90.0 mg
Sodium chloride (isotonic agent)	117.0 mg

Annexed vial (Diluent):

Diluent	Quantity
Sterile Water for Injection	10 mL

The product contains approximately 25 IU per mL of human coagulation factor VIII when reconstituted with 10 mL of diluent.

The product contains traces of von Willebrand factor.

3. PHARMACEUTICAL FORM

Lyophilized powder for injection.

- White or pale yellow, powder or friable solid.
- Reconstituted solution: clear, colorless or slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Green VIII is indicated for the treatment and prophylaxis of bleeding in patients with Hemophilia A (congenital factor VIII deficiency). (Please refer 4.4.4 General precautions)

Green VIII may be used for the management of bleeding during surgical procedures.(Please refer 4.4.4 General precautions)

Green VIII does not contain von Willebrand factor in pharmacologically effective amounts and is therefore not indicated in von Willebrand disease.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Posology

The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma.

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by <x% of normal activity> <x-y IU/dl>.

The required dose is determined using the following formula:

Required units = body weight {kg} x desired factor VIII rise {%%} (IU/dl) x {reciprocal of observed}

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in <% of normal><IU/dl>) in the corresponding period. The following table can be used to guide dosing in bleeding episodes

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%)(IU/dl)	Frequency of dose (hour)/ Duration of therapy (days)
Haemorrhage Early haemathorsis, muscle bleeding or oral bleeding	20-40	Repeat every 12-24 hours. At least 1 day, until the bleeding episode as indicated by pain is

		resolved or healing is achieved
More extensive haemathorsis, muscle bleeding or haematoma	30-80	Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
Life threatening	60-100	Repeat infusion every 8-24 hours until threat is resolved.

Prophylaxis

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

[250 IU]

Usually 250–2,000 IU is reconstituted with 10 mL diluent (water for injection) and injected intravenously or by drip-infusion at an infusion rate not exceeding 5 mL/min. Each dose can be adjusted according to weight, age, and patient condition.

Method of administration: Intravenous use

It is advisable to infuse the product at a rate not exceeding 5 mL per minute. For instructions on dilution of the medicinal product before administration, see section “Special precautions for disposal and other handling.”

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in List of Excipients.

4.4 Special warnings and precautions for use

4.4.1 Warning

Green-VIII inj., prepared from human plasma and with current scientific basis, the risk of viral infection from blood-borne virus or other pathogens (theoretically, CJD) cannot be entirely eliminated. Accordingly, proper vaccines such as Hepatitis A, etc., are recommended to patient with hemophilia or patient with immunodeficiency and doctor should regularly monitor the possibility of infection of patient. In addition, as the risk of viral infection transmission cannot be entirely eliminated due to fact that the raw material is from human plasma, explanation should be given to patient. After thorough review of the necessity of the use, minimum usage should be considered.

4.4.2 Special precautions

- 1) Patients with IgA deficiency (This product may cause anaphylaxis to patients containing anti-IgA)
- 2) Patients with hemolytic anemia or anemia from blood loss (human parvovirus B19 infection may occur. In case of B19 infection, critical systemic symptoms with fever and acute severe anemia may occur.)
- 3) Patients with immunological incompetence or immunodeficiency (human parvovirus B19 infection may occur. In case of infection, continuous anemia may occur.)

4.4.3 Precautions

- 1) Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

- 2) Hypersensitivity

Allergic-type hypersensitivity reactions are possible with Green-VIII-JAKEL inj. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented.

- 3) Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

- 4) Cardiovascular event

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

5) Viral Safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). It is strongly recommended that every time that Green-VIII-JAKEL inj. is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.4.4 General precautions

- 1) The risk of Non-A, Non-B hepatitis cannot be excluded. Patients should be monitored for liver disease for proper treatment.
- 2) Anaphylactic symptoms may occur. Accordingly, cautions should be taken before next administration.
- 3) Patients should be observed closely for signs or symptoms of coagulation inhibitor formation by repeated administration.
- 4) Since Green-VIII-JAKEL inj. contains fibrinogen in its composition, the density of fibrinogen could be extremely raised.
- 5) Hemolytic anemia may occur occasionally when administered to patients with A, B or AB blood type.
- 6) Current plasma fractionation process cannot entirely eliminate or inactivate viruses (human parvovirus B19, etc.). Accordingly, there is possibility of virus infection from administration of this product. Special cautions should be taken after administration.
- 7) Even though safety plan for the prevention of the spread of infection is prepared, risk of infection cannot be entirely disregarded since this product originated from human blood. This should be explained to patients.
- 8) Clinical trial data are not available for prophylaxis of bleeding in previously treated haemophilia A patients (PTPs), previously untreated haemophilia A patients (PUPs), and patients undergoing surgical procedures. The administration of Green-VIII-JAKEL injection should be based on a risk-benefit assessment. Data on treatment of 20 children for the treatment of bleeding in previously treated patients (PTPs) with haemophilia A (congenital factor VIII deficiency) aged below 12 years of age are available.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.6.1 Geriatric Use

Since elderly patients generally have low physiological function, this product should be administered with special care.

4.7 Effects on ability to drive and use machines

Green-VIII-JAKEL inj. has no influence on the ability to drive and use machines.

4.8 Undesirable Effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Green-VIII inj. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

For safety information with respect to transmissible agents, see section “Special warnings and precautions for use”.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequency is based on studies with all FVIII products which included patients with severe haemophilia A.

Frequencies have been evaluated according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Preferred term(s)	Frequency
Immune system disorders	Hypersensitivity	Uncommon to Rare
	Anaphylactic shock	Rare
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
Vascular disorders	Flushing	Rare
	Hypertension	Rare
Gastrointestinal disorders	Nausea, Vomiting	Rare
General disorders and administration site conditions	Pyrexia	Uncommon
	Fatigue	Uncommon

	Injection site reactions	Common
Blood and lymphatic system disorders	FVIII inhibition	Uncommon (PTPs)-
Investigations	Anti-factor VIII antibody positive	Unknown†

† One case was reported in post-marketing surveillance from Green-VIII inj. launch to July 2025.

PTPs = previously-treated patients

Description of selected adverse reactions

- Hypersensitivity: Fever, hot flush, urticaria or anaphylactic symptoms may occur.
- Liver: Liver disease may occur.
- Digestive system: Vomiting, nausea or abdominal pain may occur.
- Neuropsychiatric system: Malaise, dysphoria or headache may occur.
- Injection site: Vascular pain may occur.
- Others: Hemolytic anemia, blood pressure increase, chills, back pain, chest discomfort or hyperemia conjunctiva may occur.

4.9 Overdose

There is no experience with overdoses of Green-VIII inj.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factor VIII, ATC code: B02BD02. The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin, after which thrombin converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles, or internal organs, either spontaneously or following accidental or surgical trauma. By replacement therapy, the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and restoration of coagulation function.

In Study GC8I.LSK, a Phase I/II/III clinical study, the pharmacodynamic and clinical effects of Green-VIII were evaluated in previously treated patients (PTPs) with haemophilia A. In the Stage II on-demand part of the study, 51 PTPs were evaluated for the treatment of bleeding episodes, including 20 PTPs aged below 12 years. Clinical trial data are not available for prophylaxis in PTPs, previously untreated patients (PUPs), or patients undergoing surgical procedures.

Hemostatic efficacy was evaluated based on the physician's final assessment, which was the primary efficacy outcome, and patient's own assessments. The physician's final assessment of hemostatic effect was reported as "Good" in all subjects. The protocol-defined efficacy rate was 90.22% for acute bleeding, 54.10% for major bleeding, and 87.80% overall.

Patient's own assessments also supported the hemostatic effect of Green-VIII during on-demand treatment. Among 849 acute bleeding episodes, 20 episodes were assessed as "Excellent" and 735 episodes were assessed as "Good." The efficacy rate was 88.93% for patient's own assessment. In addition, 151 recovery assessments were performed in 51 subjects, with 5 assessments rated as "Excellent" and 136 assessments rated as "Good.". The efficacy rate only for patient's own assessment of regular visit was 93.38%.

FVIII consumption was evaluated during the treatment of bleeding episodes. A total of 967 infusions were administered for 849 acute bleeding episodes, with an average of 1.14 infusions per episode. For 61 major bleeding episodes, 112 infusions were administered, with an average of 1.84 infusions per episode. The average monthly FVIII consumption did not show notable variation.

Incremental in vivo recovery of factor VIII was assessed at baseline, 3-month, and 6-month visits to evaluate the consistency of pharmacodynamic response with repeated administrations. No statistically significant changes in incremental recovery were observed across these time points ($p = 0.4628$), indicating maintenance of the pharmacodynamic response over the course of the study.

5.2 Pharmacokinetic properties

In Stage I of Study GC8I.LSK, pharmacokinetic parameters were evaluated following administration of Green-VIII. Following administration, pharmacokinetic evaluation demonstrated measurable plasma exposure of factor VIII, with a mean maximum activity (C_{max}) of 188.67 ± 43.02 and a time to maximum activity (T_{max}) of 0.17 hours. The mean half-life ($t_{1/2}$) was 11.77 ± 3.81 hours, and the mean area under the activity-time curve from 0 to 48 hours (AUC_{0-48}) was 1883.21 ± 332.65 . The mean incremental in vivo recovery of factor VIII was $174.05 \pm 45.79\%$.

In a single-blind, randomized, cross-over pharmacokinetic (PK) study conducted in patients with severe hemophilia A, the PK profiles of GVIII and Koate DVI were compared following a single intravenous dose of 50 IU/kg.

In Period 1 ($N=6$), GVIII demonstrated a significantly lower volume of distribution (V_d) (0.372 ± 0.038 vs. 0.588 ± 0.466 mL/kg, $p=0.0022$) and higher AUC_{0-48} (2080.19 ± 344.57 vs. 1378.07 ± 443.32 IU·h/dL, $p=0.0260$), indicating greater systemic exposure than Koate DVI. No statistically significant differences were observed in C_{max} , $t_{1/2}$, or in vivo recovery between the two products.

In the combined analysis ($N=12$), GVIII maintained comparable PK parameters with Koate DVI. While a trend toward higher AUC_{0-48} and lower V_d was observed, these differences were not statistically significant ($p>0.05$). The mean in vivo recovery was similar between the two products (GVIII: $174.05 \pm 45.79\%$; Koate DVI: $158.66 \pm 30.146\%$).

5.3 Preclinical safety data (GVIII)

Factor VIII is a naturally occurring coagulation protein in the human body with a longstanding clinical use history and established safety profile. Therefore, additional non-clinical safety testing for Green-VIII-JAKEL 250 IU Powder and Solvent for Solution for Infusion is not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Powder:	Sodium Citrate
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	Calcium Chloride
	Glycine
	Sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

30 months from the date of manufacture.

6.4 Special precautions for storage

Store at 2–8°C without freezing in hermetic container.

Please refer to storage after reconstitution in section “**Special precautions for disposal and other handling.**”

6.5 Nature and contents of container

250 IU/vial (Type I glass, chlorobutyl rubber stopper and aluminium cap)

10 mL Water for Injection (Diluent) (Type I clear glass vial, chlorobutyl rubber stopper and aluminium flip-off cap).

6.6 Special precautions for disposal and other handling

- 1) Palpitations or cyanosis may occur if infusion rate is fast. Infusion rate should be as slow as possible. Patients should be observed closely for signs or symptoms of intravascular thrombosis or coagulation caused by injection of a large quantity.
- 2) Do not use if precipitate is observed when reconstituted, and also avoid combining with other preparations.
- 3) Use immediately after reconstitution. Do not use remaining solution for concerns of virus contamination. (As proteins are good environment for bacterial growth and it does not contain preservative).

7. MANUFACTURER

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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION OF THE TEXT

October 2026