ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ROCTAVIAN 2×10^{13} vector genomes/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Valoctocogene roxaparvovec is a gene therapy medicinal product that expresses the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). It is a non-replicating recombinant adeno-associated virus serotype AAV5 based vector containing the cDNA of the B-domain deleted SQ form of human coagulation factor VIII gene under the control of a liver-specific promoter.

Valoctocogene roxaparvovec is produced in a baculovirus expression system that derived from cells of *Spodoptera frugiperda* (Sf9 cell line) by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each mL of valoctocogene roxaparvovec solution for infusion contains 2×10^{13} vector genomes.

Each vial contains 16×10^{13} vector genomes of valoctocogene roxaparvovec in 8 mL solution.

Excipient with known effect

This medicinal product contains 29 mg sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless to pale yellow solution with a pH of 6.9 - 7.8 and an osmolarity of 364 - 445 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. This medicinal product should be administered in a setting where personnel and equipment are immediately available to treat infusion-related reactions (see sections 4.4 and 4.8).

ROCTAVIAN should only be administered to patients who have demonstrated absence of anti-AAV5 antibodies by a validated assay.

Posology

The recommended dose of ROCTAVIAN is 6×10^{13} vector genomes per kilogram (vg/kg) body weight, administered as a single intravenous infusion.

Calculating the patient's dose in millilitres (mL) and number of vials required

- Calculation of patient's dose volume in mL:

Body weight in kg multiplied by 3 = dose in mL

The multiplication factor 3 represents the per kilogram dose (6×10^{13} vg/kg) divided by the amount of vector genomes per mL of the ROCTAVIAN solution (2×10^{13} vg/mL).

- Calculation of number of vials to be thawed:

Patient's dose volume (mL) divided by 8 = number of vials to be thawed (round up to next whole number of vials).

The division factor 8 represents the minimum volume of ROCTAVIAN extractable from a vial (8 mL).

Table 1: Example of dose volume and number of vials to be thawed

Patient weight	**Patient's dose volume (mL) (body weight multiplied by 3)**	**Number of vials to be thawed (dose volume divided by 8, then rounded up)**
70 kg	210 mL	27 vials (rounded up from 26.25)

Discontinuation of factor VIII concentrates/haemostatic agents

When discontinuing factor VIII concentrates/haemostatic agents, physicians should consider the following:
- Patient's factor VIII activity levels are sufficient to prevent spontaneous bleeding episodes.
- The duration of effect of factor VIII concentrates/haemostatic agents.

Special populations

Hepatic impairment
The safety and efficacy of valoctocogene roxaparvovec in patients with hepatic disorders have not been established. Valoctocogene roxaparvovec is contraindicated in patients with acute or uncontrolled chronic hepatic infections, or in patients with known significant hepatic fibrosis, or cirrhosis (see section 4.3). This medicinal product is not recommended for use in patients with other hepatic disorders (see section 4.4).

Renal impairment
No dose adjustments are recommended in patients with renal impairment.

Elderly
No dose adjustments are recommended in elderly patients. Limited data are available in patients aged 65 years and older.

Paediatric population
The safety and efficacy of ROCTAVIAN in children and adolescents less than 18 years of age have not yet been established. No data are available.

Method of administration

ROCTAVIAN must be administered via intravenous infusion. Do not infuse as an intravenous push or bolus.

Administer this medicinal product in a setting where personnel and equipment are immediately available to treat infusion-related reactions (see sections 4.4 and 4.8).

ROCTAVIAN administration can begin at an infusion rate of 1 mL/min, which can be increased every 30 minutes by 1 mL/min to up to a maximum rate of 4 mL/min. The infusion rate may be slowed or interrupted if the patient develops an infusion related reaction (see section 4.4).

For detailed instructions on the preparation, administration, and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active infections, either acute or uncontrolled chronic; or patients with known significant hepatic fibrosis, or cirrhosis (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Patients with pre-existing antibodies to the AAV5 vector capsid

Experience in patients with pre-existing antibodies to the AAV5 vector capsid is limited.
Studies 270-201 and 270-301 excluded patients with detectable anti-AAV5 antibodies at screening (see section 5.1).

Anti-AAV5 antibody formation can take place after natural exposure. As it is not yet known whether or under what conditions valoctocogene roxaparvovec can be safely and effectively administered in the presence of anti-AAV5 antibodies, this medicinal product is not indicated for use in patients with detectable anti-AAV5 antibodies. Before administration, the absence of antibodies to AAV5 must be demonstrated using an appropriately validated assay (see sections 4.1 and 4.2)

Hepatic reactions and potential impact of hepatic disorders or hepatotoxic substances

Hepatic disorders and hepatotoxic substances

There is limited experience in patients with hepatic disorders or receiving potentially hepatotoxic medicinal products (see section 5.1). Safety and efficacy of ROCTAVIAN in these circumstances have not been established. The efficacy of valoctocogene roxaparvovec relies on hepatocellular expression of hFVIII-SQ. It is not known to what extent a reduced number of transducible liver cells (e.g., due to cirrhosis) or loss of transduced liver cells over time (e.g., due to active hepatitis or exposure to hepatotoxic agents) may affect the therapeutic effect of valoctocogene roxaparvovec.

Valoctocogene roxaparvovec is contraindicated in patients with acute or uncontrolled chronic hepatic infections, or in patients with known significant hepatic fibrosis, or cirrhosis (see section 4.3). This medicinal product is not recommended in patients with other hepatic disorders, hepatic laboratory abnormalities (ALT, AST, GGT, or total bilirubin above 1.25 times ULN based on at least 2 measurements, or INR of 1.4 or above) or in patients with a history of hepatic malignancy (see Hepatic function and factor VIII monitoring). Patients should be screened for hepatic malignancy prior to prescribing valoctocogene roxaparvovec.

Before using this medicinal product in patients with any hepatic disorder or receiving potentially hepatotoxic medications, physicians should consider the potential for reduced therapeutic effect and more serious hepatic reactions and the potential need to change concomitant medicinal products, allowing time for a washout period as needed (see sections 4.5 and 4.8).

The effect of alcohol consumption on the magnitude and duration of the therapeutic effect is not known. In clinical studies, some ALT elevations have been attributed to alcohol consumption. It is recommended that patients abstain from consuming alcohol for at least one year after administration of this medicinal product and, thereafter limit alcohol use.

Hepatic reactions

Following administration of valoctocogene roxaparvovec, the majority of patients (83%) experienced hepatic reactions indicated by an increase in ALT (see section 4.8); some of these reactions were temporally associated with decreased expression of the factor VIII transgene protein. The mechanism of these reactions has not yet been established.

ALT and factor VIII activity levels should be monitored after valoctocogene roxaparvovec administration (see Hepatic function and factor VIII monitoring), and corticosteroid treatment should be instituted in response to ALT elevations as needed, to control hepatic reactions and prevent or mitigate a potential reduction in transgene expression.

When establishing indication and timing of valoctocogene roxaparvovec administration for an individual patient, physicians should ensure the availability of the patient for close monitoring of hepatic laboratory parameters and factor VIII activity after administration and verify that the risks associated with the corticosteroid regimen are acceptable for the individual patient. Experience with regimens using other immunosuppressive agents is limited (see section 4.8).

Factor VIII assays

Factor VIII activity produced by ROCTAVIAN in human plasma is higher if measured with one-stage clotting assays (OSA) compared to chromogenic substrate assays (CSA). In clinical studies, there was a high correlation between OSA and CSA factor VIII activity levels across the entire range of each assay's results. For routine clinical monitoring of factor VIII activity levels, either assay may be used. The conversion factor between the assays can be approximated based on clinical study results to be: OSA = 1.5 × CSA. For example, a factor VIII activity level of 50 IU/dL using CSA calculates to a level of 75 IU/dL using OSA. The following central laboratory tests were used in clinical studies: ellagic acid for OSA (similar results were obtained for silica and kaolin) and bovine factor IX for CSA (similar results were obtained for human factor IX).

When switching from haemostatic products (e.g., emicizumab) prior to valoctocogene roxaparvovec therapy, physicians should refer to the relevant product information to avoid the potential for factor VIII activity assay interference during the transition period.

Hepatic function and factor VIII monitoring

In the first year after ROCTAVIAN administration, the purpose of hepatic and factor VIII monitoring is to detect increases in ALT, which may be accompanied by decreased factor VIII activity and may indicate the need to initiate corticosteroid treatment (see sections 4.2 and 4.8). Following the first year of administration, hepatic and factor VIII monitoring is intended to routinely assess liver health and bleeding risk, respectively.

A baseline assessment of liver health (including liver function tests within 3 months and recent fibrosis assessment using either imaging modalities, such as ultrasound elastography, or laboratory assessments, within 6 months) should be obtained before administration of ROCTAVIAN. Consider obtaining at least two ALT measurements prior to administration, or use an average of prior ALT measurements to establish patient's baseline ALT. It is recommended that the hepatic function is evaluated through a multidisciplinary approach with involvement of a hepatologist to best adjust the monitoring to the patient's individual condition.

It is recommended (where possible) to use the same laboratory for hepatic testing at baseline and monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

After administration, the patient's ALT and factor VIII activity levels should be monitored according to Table 2. To assist in the interpretation of ALT results, monitoring of ALT should be accompanied by monitoring of aspartate aminotransferase (AST) and creatine phosphokinase (CPK) to help rule out alternative causes for ALT elevations (including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise). Based on patient's ALT elevations, corticosteroid treatment may be indicated (see Corticosteroid treatment). Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering.

It should be ensured the availability of the patient for frequent monitoring of hepatic laboratory parameters and factor VIII activity after administration.

Table 2: Hepatic function and factor VIII activity monitoring

	Measurements	Timeframe	Monitoring frequency[a]
Before administration	Liver function tests Recent fibrosis assessment	Within 3 months prior to infusion Within 6 months prior to infusion	Baseline measurement
After administration	ALT and factor VIII activity[b]	First 26 weeks	Weekly
		Weeks 26 to 52 (Year 1)	Every 2 to 4 weeks
		Year 1 to end of Year 2	• Every 3 months for patients with factor VIII activity levels > 5 IU/dL • Consider more frequent monitoring in patients with factor VIII activity levels ≤ 5 IU/dL and consider the stability of factor VIII levels and evidence of bleeding.
		After Year 2	• Every 6 months for patients with factor VIII activity > 5 IU/dL • Consider more frequent monitoring in patients with factor VIII activity levels ≤ 5 IU/dL and consider the stability of factor VIII levels and evidence of bleeding.

[a] Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering. Adjustment of the monitoring frequency may also be indicated depending on the individual situation.
[b] Monitoring of ALT should be accompanied by monitoring of AST and CPK, to rule out alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise).

If a patient returns to prophylactic use of factor VIII concentrates/haemostatic agents for haemostatic control, consider following monitoring and management consistent with instructions for those agents. An annual health check-up should include liver function tests.

Variability of factor VIII activity

Inter-patient factor VIII activity level variability was observed after administration with no identified potential factors of variability. In study 270-301, inter-patient variability could not be explained by patient baseline characteristics, demographics, or other predictive factors. Some patients might have low factor VIII activity levels following ROCTAVIAN treatment, but could still derive a clinical benefit in terms of a reduction of exogenous factor VIII requirement and annualised bleeding rates. A trend of lower factor VIII activity levels was observed in Black patients within the study population. Given the small sample size, the limited number of sites enroling Black patients relative to the total population, the existence of potential confounding factors, and multiple post-hoc analyses, this trend was insufficient to allow meaningful conclusions about the differences in response rates based on race or other factors therein influencing factor VIII expression following valoctocogene roxaparvovec

infusion. Despite differences in factor VIII activity levels, ABR and annualised factor VIII usage was similar across races.

Corticosteroid treatment

In study 270-301, corticosteroids were initiated upon observed ALT elevations to dampen potential inflammatory responses and associated possible reductions in factor VIII expression. The recommended corticosteroid regimen based on current clinical experience is provided. Reference to the corticosteroid product information for risks and required precautions is recommended.

If a patient's ALT rises above 1.5 × baseline (see definition of baseline above in Hepatic function and factor VIII monitoring) or above ULN, it is recommended to evaluate alternative causes of the ALT elevation (including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise). Repeating ALT laboratory testing within 24 to 48 hours and, if clinically indicated and performing additional tests to exclude alternative etiologies should be considered, (see section 4.5). In the absence of an alternative cause for the ALT elevation, a corticosteroid regimen should be promptly initiated at a daily dose of 60 mg prednisone (or equivalent dose of another corticosteroid) for 2 weeks. The daily corticosteroid dose can be gradually tapered in a stepwise manner according to Table 3. Patients with baseline ALT levels between > ULN to 1.25 × ULN should initiate the corticosteroid regimen described in Table 3 if their ALT increases above 1.5 × baseline.

In patients who have not reached factor VIII activity levels of at least 5 IU/dL by 5 months, administration of corticosteroids did not improve factor VIII expression. There is limited benefit of initiating or extending a corticosteroid course beyond 5 months in this population, unless it is to manage significant ALT elevations or concerns about liver health.

There is limited information with regards to the benefit of starting a new corticosteroid course after the first year of ROCTAVIAN administration.

Table 3: Recommended corticosteroid regimen in response to ALT elevations

	Regimen (prednisone or equivalent dose of another corticosteroid)
Starting dose[a]	60 mg daily for 2 weeks
Tapering[b]	40 mg daily for 3 weeks 30 mg daily for 1 week 20 mg daily for 1 week 10 mg daily for 1 week

[a] If ALT continues to rise or has not improved after 2 weeks, increase the corticosteroid dose up to a maximum of 1.2 mg/kg, after ruling out alternative causes for ALT elevation.

[b] Tapering of corticosteroids can start after 2 weeks if ALT levels remain stable and/or earlier when ALT levels start to decline. The taper may be individualised based on the course of hepatic function, taking into account the patient's medical condition, corticosteroid tolerance, and potential for withdrawal symptoms.

If corticosteroids are contraindicated, other immunosuppressive therapy could be considered. It is recommended to set a multidisciplinary consultation involving a hepatologist, to best adjust the alternative to corticosteroids and the monitoring to the patient's individual condition. Physicians should also consider discontinuing corticosteroids in cases where corticosteroids are ineffective or not tolerated. There is limited experience on the use of alternative immunosuppressants (see section 4.8). If ALT has not improved despite 4 weeks on the maximum corticosteroid dose and is above 3 × ULN, alternative immunosuppressants may be considered and in addition, consider further workup for alternative causes of ALT elevation.

Investigations are ongoing to determine the optimal corticosteroid regimen.

The patient's ability to receive corticosteroids that could be required for an extended time period should be evaluated. It should be ensured that the risks associated with the described regimen are likely to be acceptable for the individual patient.

Infusion-related reactions

Infusion-related reactions to valoctocogene roxaparvovec can have multiple manifestations (such as skin, mucosal, respiratory, gastrointestinal and cardiovascular manifestations, and pyrexia) and may require reduction in infusion rate, interruption of infusion, pharmacologic intervention, and prolonged observation(see sections 4.2 and 4.8).

Patients should be monitored during and after the infusion for possible acute infusion reactions (see section 4.8). Instructions should be provided when discharging the patient to seek medical attention in case of a new or recurrent reaction.

Risk of thrombotic events

An increase in factor VIII activity may contribute to a patient's individual, multifactorial risk for venous and arterial thrombotic events. There is no experience in patients with a relevant history of venous or arterial thrombotic/thromboembolic events or known history of thrombophilia.

Some patients have experienced elevations of factor VIII activity to levels greater than the ULN (see section 4.8).

Patients should be evaluated before and after administration of valoctocogene roxaparvovec for risk factors for thrombosis and general cardiovascular risk factors. Based on factor VIII activity levels achieved, patients should be advised according to their individual condition. Patients should seek immediate medical attention if they observe signs or symptoms that may indicate a thrombotic event.

Contraceptive measures in relation to transgene DNA shedding in semen

Male patients should be informed on the need for contraceptive measures for them and their female partners of child bearing potential (see section 4.6).

Blood, organ, tissue and cell donation

There is a lack of experience with donation of blood or organs, tissues and cells for transplantation following AAV vector-based gene therapy. Therefore, patients treated with this medicinal product must not donate blood or organs, tissues or cells for transplantation. This information is provided in the Patient Card which should be given to the patient after treatment.

Immunocompromised patients

No immunocompromised patients, including patients undergoing immunosuppressive treatment within 30 days before valoctocogene roxaparvovec infusion, were enrolled in the pre-registration clinical studies. Safety and efficacy of this medicinal product in these patients have not been established. Use in immunocompromised patients is based on prescriber judgment, taking into account the patient's general health and potential for corticosteroid use post-valoctocogene roxaparvovec treatment.

HIV positive patients

Only a few HIV infected patients have been treated with valoctocogene roxaparvovec as part of the clinical studies. Among them, one patient experienced elevation in hepatic enzymes suggestive of an interaction with efavirenz in the patient's HIV treatment regimen. Given the risk of hepatotoxicity and/or effect on factor VIII expression, the HIV patient's existing antiretroviral therapy regimen

should be carefully evaluated prior to initiating treatment and following treatment with valoctocogene roxaparvovec. The physician treating the HIV infection should be consulted to consider whether a less hepatotoxic antiretroviral therapy regimen could be available and suitable for the patient, and if indicated, switch the patient to the new antiretroviral therapy regimen whenever feasible (see sections 4.5).

Patients with active infections

There is no experience with administration of ROCTAVIAN in patients with acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as chronic active hepatitis B). It is possible that such infections affect the response to valoctocogene roxaparvovec and reduce its efficacy and/or cause adverse reactions. Therefore, this medicinal product is contraindicated in patients with such infections (see section 4.3). If there are signs or symptoms of acute or uncontrolled chronic active infections, treatment must be postponed until the infection has resolved or is controlled.

Patients with factor VIII inhibitors, monitoring for inhibitors

Patients who have or had inhibitors (neutralising antibodies) to factor VIII were excluded from participation in the clinical studies. It is not known whether or to what extent such inhibitors affect the safety or efficacy of valoctocogene roxaparvovec.

All patients remained negative for factor VIII inhibitors at all time points evaluated post-infusion.

ROCTAVIAN is not indicated for use in patients with a history of factor VIII inhibitors.

After administration of valoctocogene roxaparvovec, patients should be monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests.

Use of factor VIII concentrates or haemostatic agents after treatment with valoctocogene roxaparvovec

Following administration of valoctocogene roxaparvovec:

- Factor VIII concentrates/haemostatic agents should be used in case of invasive procedures, surgery, trauma, or bleeds, consistent with current treatment guidelines for the management of haemophilia, and based on the patient's current factor VIII activity levels.
- If the patient's factor VIII activity levels are consistently below 5 IU/dL and the patient has experienced recurrent spontaneous bleeding episodes, physicians should consider the use of factor VIII concentrates/haemostatic agents to minimise such episodes, consistent with current treatment guidelines for the management of haemophilia. Target joints should be treated in accordance with relevant treatment guidelines.

Repeat treatment and impact to other AAV-mediated therapies

It is not yet known whether or under what conditions valoctocogene roxaparvovec therapy may be repeated, and to what extent cross-reacting antibodies could interact with the capsids of AAV vectors used by other gene therapies, potentially impacting their efficacy.

Risk of malignancy as a result of vector integration

Integration site analysis was performed on liver samples from 5 patients treated with ROCTAVIAN in clinical studies. Samples were collected approximately 0.5-4.1 years post-dose. Vector integration into human genomic DNA was observed in all samples.

ROCTAVIAN can also insert into DNA of other human body cells (as observed in parotid gland DNA samples from one patient treated with ROCTAVIAN in a clinical study). The clinical relevance of individual integration events is not known to date, but it is acknowledged that individual integration events could potentially contribute to a risk of malignancy (see section 5.3).

So far, no cases of malignancies associated with ROCTAVIAN treatment have been reported. In the event that a malignancy occurs, the marketing authorisation holder should be contacted to obtain instructions on collecting patient samples for integration site analysis.

Long-term follow-up

Patients are expected to be enrolled in a registry to follow haemophilia patients for 15 years, to substantiate the long-term efficacy and safety of this gene therapy.

Sodium content

This medicinal product contains 29 mg sodium per vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Prior to valoctocogene roxaparvovec administration, the patient's existing medicinal products should be reviewed to determine if they should be modified to prevent anticipated interactions described in this section.

Patients' concomitant medications should be monitored after valoctocogene roxaparvovec administration, particularly during the first year, and the need to change concomitant medicinal products based on patient's hepatic status and risk should be evaluated. When a new medication is started, close monitoring of ALT and factor VIII activity levels (e.g., weekly to every 2 weeks for the first month) is recommended to assess potential effects on both levels.

No *in vivo* interaction studies have been performed.

Hepatotoxic medicinal products or substances

Caution of use with hepatotoxic medications or hepatotoxic substances should be applied due to limited experience. The safety and efficacy of valoctocogene roxaparvovec in these circumstances have not been established (see section 4.4).

Before administering valoctocogene roxaparvovec to patients receiving potentially hepatotoxic medicinal products or using other hepatotoxic agents (including alcohol, potentially hepatotoxic herbal products and nutritional supplements) and when deciding on the acceptability of such agents after treatment with valoctocogene roxaparvovec, physicians should consider that they may reduce the efficacy of valoctocogene roxaparvovec and increase the risk for more serious hepatic reactions, particularly during the first year following valoctocogene roxaparvovec administration (see section 4.4).

Isotretinoin

In one patient, decreased factor VIII activity without ALT elevation was detected after starting treatment with systemic isotretinoin following valoctocogene roxaparvovec infusion; factor VIII activity was 75 IU/dL at week 60 and transiently decreased to < 3 IU/dL at week 64, after initiating isotretinoin. After discontinuing isotretinoin at week 72, factor VIII activity recovered to 46 IU/dL at week 122. An *in vitro* study in human primary hepatocytes indicated that isotretinoin suppressed factor VIII expression independent of hepatotoxicity. Isotretinoin is not recommended in patients who are benefiting from valoctocogene roxaparvovec.

Efavirenz

One HIV positive patient treated with an antiretroviral therapy regimen consisting of efavirenz, lamivudine, and tenofovir experienced asymptomatic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 elevations of ALT, AST, and GGT (> 5.0 × ULN) and a Grade 1 elevation of serum bilirubin (> ULN and up to 1.5 × ULN) at week 4, suggestive of an interaction with efavirenz (see section 4.4). The reaction did not respond to corticosteroid treatment but responded to withdrawal of efavirenz and resolved after his antiretroviral therapy regimen was changed to a regimen without efavirenz. The patient later reverted to prophylactic use of factor VIII concentrates/haemostatic agents. An *in vitro* study in human primary hepatocytes indicated that efavirenz suppressed factor VIII expression independent of hepatotoxicity. Efavirenz is not recommended in patients who are benefiting from valoctocogene roxaparvovec. The use of non-efavirenz treatments should be considered.

Interactions with agents that may reduce or increase plasma concentrations of corticosteroids

Agents that may reduce or increase the plasma concentration of corticosteroids (e.g., agents that induce or inhibit cytochrome P450 3A4) can decrease the efficacy of the corticosteroid regimen or increase their side effects (see section 4.4).

Vaccinations

Prior to valoctocogene roxaparvovec infusion, ensure that the patient's vaccinations are up to date. The patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy (see section 4.4). Live vaccines should not be administered to patients while on immunomodulatory therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

No dedicated animal fertility/embryofoetal studies have been conducted to substantiate whether the use in women of childbearing potential and during pregnancy could be harmful for the new-born child (theoretical risk of viral vector integration in foetal cells through vertical transmission). Moreover, no data are available to recommend a specific duration of contraceptive measures in women of childbearing potential. Therefore, ROCTAVIAN is not recommended in women of childbearing potential.

Contraception after administration to males

In clinical studies, after administration of ROCTAVIAN, transgene DNA was temporarily detectable in semen (see sections 4.4 and 5.2).

For 6 months after administration of ROCTAVIAN

- treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using double barrier contraception, and
- men must not donate semen.

Pregnancy

Experience regarding the use of this medicinal product during pregnancy is not available. Animal reproduction studies have not been conducted with ROCTAVIAN. It is not known whether this medicinal product can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. ROCTAVIAN should not be used during pregnancy.

Breast-feeding

It is unknown whether valoctocogene roxaparvovec is excreted in human milk. A risk to the new-borns/infants cannot be excluded. ROCTAVIAN should not be used during breast-feeding.

Fertility

No non-clinical or clinical studies were performed to evaluate the effect of valoctocogene roxaparvovec on fertility (see Contraception after administration to males).

4.7 Effects on ability to drive and use machines

Infusion of valoctocogene roxaparvovec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as temporary presyncope, dizziness, fatigue, and headache that have occurred shortly after valoctocogene roxaparvovec administration, patients should be advised to use caution when driving and operating machinery until they are certain that this medicinal product does not adversely affect them (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions to ROCTAVIAN were increases in ALT (83%), AST (70%), LDH (57%), and CPK (48%), nausea (37%), and headache (35%).

Tabulated list of adverse reactions

The following adverse reactions described are based on a total of 141 patients from Studies 270-201 and 270-301, all dosed at 6×10^{13} vg/kg and followed for up to 375 weeks (see section 5.1).

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are categorised as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 4: Tabulated list of adverse reactions to valoctocogene roxaparvovec

MedDRA system organ class	Adverse reaction	Frequency
Infections and infestations	Flu-like symptoms	Common
Blood and lymphatic system disorders	Factor VIII activity levels above ULN[a]	Very common
Immune system disorders	Hypersensitivity reaction[b]	Common
Nervous system disorders	Headache	Very common
	Dizziness[b]	Common
	Presyncope[b]	Uncommon
Cardiac disorders	Increased blood pressure[b]	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea[b]	Uncommon
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea	Very common
	Dyspepsia	Common
Hepatobiliary disorders[c]	ALT increased, AST increased, GGT increased, bilirubin increased, and LDH increased	Very common
Skin and subcutaneous tissue disorders	Rash[d], pruritus[b]	Common
Musculoskeletal and connective tissue disorders	CPK increased	Very common
	Myalgia	Common
General disorders and administration site conditions	Fatigue[e]	Very common
	Infusion-related reaction[f]	Common

[a] One or more instances of factor VIII activity levels > 170 IU/dL (ULN of the CSA used) or > 150 IU/dL (ULN of the OSA used). See Description of selected adverse reactions.
[b] Considered an adverse reaction only during first 48 hours after infusion.
[c] Reflects laboratory abnormalities above the ULN.
[d] Rash includes maculopapular rash and urticaria.
[e] Fatigue includes lethargy and malaise.
[f] Infusion-related reactions includes manifestations such as skin, mucosal, and respiratory tract (including urticaria, pruritus, maculopapular rash, sneezing, coughing, dyspnoea, rhinorrhoea, watery eyes, and tingling throat), gastrointestinal (including nausea and diarrhoea), cardiovascular (including increased blood pressure, hypotension, tachycardia, and presyncope) and musculoskeletal (including myalgia and lower back pain), as well as pyrexia, rigours, and chills.

Description of selected adverse reactions

Infusion-related reactions

Eleven patients (8%; 11/141) experienced infusion-related reactions with symptoms during or within 6 hours after the end of infusion that included one or more of the following: skin, mucosal, and respiratory tract manifestations (including urticaria, pruritus, maculopapular rash, sneezing, coughing, dyspnoea, rhinorrhoea, watery eyes, and tingling throat), gastrointestinal manifestations (including nausea and diarrhoea), cardiovascular manifestations (including increased blood pressure, hypotension, tachycardia, and presyncope) and musculoskeletal manifestations (including myalgia and lower back pain), as well as pyrexia, rigours, and chills. The median time to onset was 1 hour (range: 0.25, 5.87) from the start of the infusion, and median duration was 1 hour. Four patients had reactions during the infusion. Three of these patients experienced CTCAE Grade 3 hypersensitivity reaction, and temporary interruption of the infusion was required, followed by re-initiation at a slower rate. All patients who experienced infusion-related reactions completed their infusions. Seven of the 11 patients received one or more of the following medications: systemic antihistamines, corticosteroids, and/or antiemetics. In addition, 1 patient received intravenous fluids and epinephrine. All events of infusion-related reactions resolved without sequelae.

Hepatic laboratory abnormalities

Table 5 describes hepatic laboratory abnormalities following administration of ROCTAVIAN. ALT increases are further characterised, as they may be accompanied by decreased factor VIII activity and may indicate the need to initiate corticosteroid treatment (see section 4.4).

Table 5: Hepatic laboratory abnormalities in patients administered 6×10^{13} vg/kg ROCTAVIAN in studies 270-201 and 270-301

	Number of patients (%) N = 141
ALT increases > ULN	117 (83%)
CTCAE Grade 2[a]	29 (21%)
CTCAE Grade 3[b]	12 (9%)
AST increases > ULN[c]	98 (70%)
CTCAE Grade 2[a]	16 (11%)
CTCAE Grade 3[b]	10 (7%)
GGT increases > ULN[c]	25 (18%)
CTCAE Grade 2[a]	3 (2%)
CTCAE Grade 3[b]	2 (1%)
Bilirubin increases > ULN[c,d]	20 (14%)
CTCAE Grade 2[e]	4 (3%)
CTCAE Grade 3[f]	1 (1%)
LDH increases > ULN	81 (57%)

[a] CTCAE Grade 2: > 3.0 and up to 5.0 × ULN
[b] CTCAE Grade 3: > 5.0 × ULN
[c] Post baseline values are based on the highest CTCAE Grade
[d] No patients had CTCAE Grade 3 elevations
[e] CTCAE Grade 2: > 1.5 and up to 3.0 × ULN
[f] CTCAE Grade 3: > 3.0 and up to 10.0 × ULN

ALT increases

Forty-four percent of ALT increases above ULN occurred within the first 26 weeks; 29% of ALT increases occurred within week 27 to 52, and 27% of ALT increases occurred beyond 52 weeks after administration. The median duration of ALT increases above ULN was 3 weeks. Ninety-seven of the 141 patients (69%) had two or more episodes of ALT increases above ULN.

Twelve (9%) patients experienced Grade 3 ALT elevations (15 episodes total). The range of Grade 3 ALT elevations were 216 IU/dL to 623 IU/dL. The majority of Grade 3 ALT elevations (73%) occurred within the first 26 weeks, 3 (20%) occurred within week 27 to 52, and 1 (7%) occurred beyond 52 weeks after administration. All Grade 3 ALT elevations resolved with corticosteroids, including 2 patients that received IV methylprednisolone.

In the patients who had ALT increases above ULN, the median (range) time to initial reduction in ALT (defined as first drop of at least 10 U/L or ALT ≤ ULN) following a new corticosteroid course or increase in corticosteroid dose was 8 (2, 71) days.

Immunosuppressant use to prevent or mitigate ALT elevations

In study 270-301, 106 of the 134 patients (79%) received corticosteroid (prednisone or prednisolone) treatment in response to ALT elevations starting at a median of 8 weeks after ROCTAVIAN administration. The majority of these patients (93%; 99 out of 106) started corticosteroid treatment within the first 26 weeks, 6 patients (6%) started corticosteroid treatment between weeks 26 and 52, and 1 patient started corticosteroid treatment after 52 weeks. The range in the timing for initiating corticosteroids was driven by the variability in time of first ALT elevation among patients and differences in the defined ALT threshold criteria for initiating corticosteroids that changed over the course of the study. The median (range) total duration of corticosteroid use (including repeat treatment) was 33 (3, 120) weeks. A prolonged corticosteroid regimen was also observed in patients not achieving factor VIII activity level > 5 IU/dL (low responders). Extending the duration of corticosteroid treatment did not result in significant benefit to factor VIII levels (see section 4.4).

In study 270-301, patients received alternative immunosuppressants (AIS) other than prednisone or prednisolone, due to inability to tolerate corticosteroids or ineffectiveness of corticosteroids. Nineteen (14%) patients had their ALT levels above ULN prior to receiving AIS. These medications included one or more of the following: tacrolimus, mycophenolate, and budesonide.
IV methylprednisolone was administered in 2 patients for Grade 3 ALT elevations.

An open-label study (270-303) was conducted in 22 patients to evaluate the effects of a prophylactic corticosteroid treatment starting on the day of the ROCTAVIAN infusion. Patients receiving prophylactic corticosteroids had lower factor VIII activity levels at week 52 compared to patients in study 270-301. This prophylactic corticosteroid treatment was associated with fewer ALT increases above ULN; however, the severity grade of ALT increases were similar to those observed with the reactive corticosteroid treatment used in study 270-301 and recommended in section 4.4.

Factor VIII activity levels above ULN

In studies 270-201 and 270-301, there were patients with one or more instances of factor VIII activity levels above ULN (see Table 6 and section 4.4). Two patients had transient factor VIII activity levels above the assays limit of quantitation (> 463 IU/dL for CSA and > 500 IU/dL for OSA). One patient received enoxaparin for venous thromboembolism prophylaxis based on that patient's individual risk factors. Three of 38 (8%) patients in study 270-301 and none of the patients in study 270-201 had their factor VIII activity levels remain above ULN at the time of the data cut.

Table 6: Factor VIII activity levels above ULN[a]

	Study 270-301 ITT Population (N = 134)		Study 270-201 6×10^{13} vg/kg Cohort (N = 7)	
	OSA	**CSA**	**OSA**	**CSA**
Proportion of patients n (%)	38 (28%)	16 (12%)	4 (57%)	2 (29%)
Time to first factor VIII measure > ULN (weeks)				
Mean (SD)	15.2 (7.8)	18.1 (6.0)	22.4 (8.5)	24.7 (4.9)
Median (Range)	13.4 (6.1, 44.1)	18.1 (8.3, 29.1)	20.1 (15.3, 34.1)	24.7 (21.3, 28.1)
Duration of factor VIII measures > ULN (weeks)				
Mean (SD)	37.4 (52.7)	31.2 (48.5)	34.8 (33.0)	2.4 (0.5)
Median (Range)	11.8 (0.7, 197.7)	13.5 (0.7, 167.0)	31.2 (2.3, 74.6)	2.4 (2.0, 2.7)

[a] ULN of > 150 IU/dL for OSA and ULN of > 170 IU/dL for CSA.

Immunogenicity

In studies 270-201 and 270-301, all patients receiving treatment were required to screen negative for anti-AAV5 antibodies and negative (< 0.6 BU) for factor VIII inhibitors in a Nijmegen modified Bethesda assay following a lifetime minimum of 150 exposure days to factor VIII replacement therapy (see sections 4.1 and 4.4).

Following infusion of ROCTAVIAN, all patients remained negative for factor VIII inhibitors at all time points evaluated post-infusion by the time of the data cut.

All patients seroconverted to anti-AAV5 antibody positive within 8 weeks of administration. Mean anti-AAV5 total antibody titres peaked by 36 weeks after administration and remained stable until the last time point tested.

ROCTAVIAN-treated patients were tested for cellular immune responses against the AAV5 capsid and the factor VIII transgene product using an IFN-γ ELISpot assay. AAV5 capsid-specific cellular immune responses were detected beginning at week 2 following dose administration and often declined or reverted to negative over the first 52 weeks in the majority of patients with available data.

Factor VIII-specific responses were detected in fewer subjects, often sporadically at a single time point and reverting to negative in most patients. No association between factor VIII cellular immune response and ALT or factor VIII activity measures could be established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with accidental infusion of too high a dose volume. If considered necessary, treatment of an overdose should be symptomatic and supportive. Receiving higher doses than recommended may result in higher factor VIII activity levels and may theoretically be associated with increased risk of thrombotic events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagic, blood coagulation factors, ATC code: B02BD15

Mechanism of action

Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) based gene therapy vector causing the expression of the B-domain deleted SQ form of a recombinant human factor VIII (hFVIII-SQ) under the control of a liver-specific promoter. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective haemostasis. Following valoctocogene roxaparvovec infusion, vector DNA is processed *in vivo* to form full-length, episomal transgenes that persist as the stable DNA forms that support long-term production of hFVIII-SQ.

Pharmacodynamic effects

The pharmacodynamic effect of valoctocogene roxaparvovec was assessed by circulating factor VIII activity levels (see subsection Clinical efficacy and safety below).

Clinical efficacy and safety

The efficacy of a single intravenous infusion of 6×10^{13} vg/kg valoctocogene roxaparvovec was evaluated in a Phase 3 open-label single-arm study (study 270-301) in adult males (18 years of age and older) with severe haemophilia A (residual factor VIII activity ≤ 1 IU/dL). Patients had been treated with prophylactic factor VIII replacement therapy for at least 12 months prior to study entry and exposed to factor VIII concentrates.

The study excluded patients with active hepatitis B or C infection, prior liver biopsy showing significant fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent), known hepatic cirrhosis, or history of hepatic malignancy. Except for elevated total bilirubin in 2 patients with Gilbert's syndrome, ALT, AST, GGT, bilirubin and alkaline phosphatase was normal or below $1.25 \times$ ULN in study 270-301. Detectable antibodies to AAV5 at screening, active infections, and/or history of venous or arterial thrombotic/thromboembolic events (outside of catheter-associated thromboses) or known thrombophilia were exclusion criteria in study 270-301. Patients with an immunocompromised state (including patients on immunosuppressive medication) were excluded. See section 4.4.

In study 270-301, 134 patients (intent-to-treat population; ITT), aged 18 to 70 years (median: 30 years; 1 patient (0.7%) was ≥ 65 years), received 6×10^{13} vg/kg of ROCTAVIAN with follow-up ranging from 66 to 266 weeks (mean: 221 weeks). The population was 72% White (96 patients), 14% Asian (19 patients), 11% Black (15 patients), and 3% Other or not specified. One hundred thirty-two (132) patients were HIV-negative (modified intent-to-treat population; mITT). One hundred twelve (112) patients previously participated in a non-interventional study (NIS) with at least 6 months of prospectively collected baseline data prior to enrolment in study 270-301. One hundred six of the 134 patients initiated corticosteroid treatment only in response to ALT elevation (generally starting at 60 mg/day and gradual tapering thereafter); see section 4.8.

The primary efficacy endpoint was change in factor VIII activity at week 208 post-ROCTAVIAN infusion from baseline (imputed as 1 IU/dL), as measured by CSA. The secondary efficacy endpoints were change from baseline in ABR requiring exogenous factor VIII and annualised use of exogenous factor VIII in the post-factor VIII prophylaxis period.

Factor VIII activity

Factor VIII activity levels (IU/dL) over time post-ROCTAVIAN infusion are reported in Table 7 by both the CSA and OSA. The following central laboratory tests were used in clinical studies: ellagic acid for OSA (similar results were obtained for silica and kaolin) and bovine factor IX for CSA (similar results were obtained for human factor IX). The time profile of factor VIII activity is generally characterised by a tri-phasic response with rapid increase within approximately the first 6 months, followed by an initial decline, and then a more gradual decline thereafter.

Table 7: Factor VIII activity levels (IU/dL) over time in patients with severe haemophilia A[a] (ITT population; N = 134)

Timepoint	Patients (n)	Factor VIII activity level (IU/dL)[b]	
		CSA	OSA
Month 6 Mean (SD) Median (Range)	134	52.6 (54.8) 38.1 (0, 367.3)	80.8 (79.5) 60.5 (1.8, 483.9)
Month 12 Mean (SD) Median (Range)	134	42.4 (45.3) 23.9 (0, 231.2)	63.4 (64.5) 40.2 (0, 311.1)
Month 18 Mean (SD) Median (Range)	134	26.1 (30.8) 13.2 (0, 167.9)	38.6 (44.1) 21.4 (0, 232.2)
Month 24 Mean (SD) Median (Range)	134	22.7 (32.9) 11.6 (0, 187.1)	35.5 (47.2) 21.3 (0, 271.3)
Month 36 Mean (SD) Median (Range)	134	18.2 (30.6) 8.2 (0, 217.7)	27.8 (40.7) 16.0 (0, 291.4)
Month 48 Mean (SD) Median (Range)	132[c]	15.8 (28.7) 6.5 (0, 197.9)	26.7 (45.5) 13.2 (0, 306.9)

[a] Patients with residual factor VIII ≤ 1 IU/dL as evidenced by medical history.

[b] Based on the median factor VIII activity level measures taken during weeks 23 to 26 for month 6, during weeks 49 to 52 for month 12, a 4-week window around week 76 for month 18, a 4-week window around week 104 for month 24, a 6-week window around week 156 for month 36, and a 6-week window around week 208 for month 48.

[c] Two patients in the ITT population did not reach month 48 as of the data cut.

The proportion of patients achieving factor VIII activity level thresholds by year are presented in Table 8 by both the CSA and OSA. The majority (95%) of patients who reach factor VIII activity levels of ≥ 5 IU/dL do so within 5 months post-infusion.

Table 8: Patients achieving factor VIII activity thresholds by year (ITT population; N = 134)

Factor VIII activity threshold achieved by assay[a]	**Year 1** N = 134 n (%)	**Year 2** N = 134 n (%)	**Year 3** N = 134 n (%)	**Year 4** N = 132[b] n (%)
CSA				
> 150 IU/dL	7 (5%)	2 (1%)	2 (1%)	2 (2%)
40 - ≤ 150 IU/dL	42 (31%)	19 (14%)	12 (9%)	8 (6%)
15 - < 40 IU/dL	46 (34%)	33 (25%)	26 (19%)	29 (22%)
5 - < 15 IU/dL	23 (17%)	45 (34%)	47 (35%)	39 (30%)
3 - < 5 IU/dL	3 (2%)	14 (10%)	14 (10%)	18 (14%)
< 3 IU/dL[c]	13 (10%)	21 (16%)	33 (25%)	36 (27%)
OSA				
> 150 IU/dL	13 (10%)	5 (4%)	3 (2%)	4 (3%)
40 - ≤ 150 IU/dL	55 (41%)	31 (23%)	22 (16%)	18 (14%)
15 - < 40 IU/dL	43 (32%)	45 (34%)	45 (34%)	39 (30%)
5 - < 15 IU/dL	13 (10%)	31 (23%)	36 (27%)	41 (31%)
1 - < 5 IU/dL	8 (6%)	14 (10%)	16 (12%)	15 (11%)
< 1 IU/dL[c]	2 (1%)	8 (6%)	12 (9%)	15 (11%)

[a] Based on the median of factor VIII activity level measures taken during weeks 49 to 52 for year 1, a 4-week window around week 104 for year 2, a 6-week window around week 156 for year 3, and a 6-week window around week 208 for year 4.

[b] Two patients in the ITT population did not reach year 4 as of the data cut.

[c] 3 IU/dL is the lower limit of quantitation of the CSA used and 1 IU/dL is the lower limit of quantitation of the OSA used.

Annualised bleeding rate (ABR) and annualised use of exogenous factor VIII

Table 9 describes the ABR and exogenous factor VIII use results following ROCTAVIAN treatment in study 270-301 for the patients previously enrolled in the non-interventional study.

Table 9: ABR and annualised factor VIII usage at baseline and post-factor VIII prophylaxis

		Study 270-301 Patients from non-interventional study (NIS) N = 112	
		Baseline	**Post-factor VIII prophylaxis period**
Duration of data collection (week)	Mean (SD) Median (Range)	36.5 (9.4) 32.9 (26, 68)	210.5 (19.5) 209.4 (88, 242)
ABR (bleeds/year) for bleeds treated with exogenous factor VIII replacement			
Overall[a]	Mean (SD) Median (Range)	4.8 (6.5) 2.8 (0, 33.1)	0.8 (2.0) 0 (0, 12.0)
	Change from baseline Mean (SD) 95% CI	-4.0 (6.5) -5.2, -2.8	
	Patients with 0 bleeds	32%	54%
Joint bleeds	Mean (SD) Median (Range)	2.8 (4.3) 1.4 (0, 23.1)	0.5 (1.3) 0 (0, 6.5)
	Patients with 0 bleeds	44%	68%
Target joint bleeds[b]	Mean (SD) Median (Range)	0.5 (1.6) 0 (0, 9.2)	0.1 (0.7) 0 (0, 5.1)
	Patients with 0 bleeds	88%	94%

Spontaneous bleeds	Mean (SD) Median (Range)	2.0 (3.5) 0 (0, 21.3)	0.4 (1.1) 0 (0, 6.8)
	Patients with 0 bleeds	55%	71%
Annualised factor VIII usage			
Infusion rate (infusions/year)	Mean (SD) Median (Range)	135.9 (52.0) 128.6 (39.5, 363.8)	6.1 (15.6) 0.6 (0, 109.7)
	Change from baseline Mean (SD) 95% CI	-129.8 (51.6) -139.4, -120.1	
Utilisation rate (IU/kg/year)	Mean (SD) Median (Range)	3961 (1751) 3754 (1296, 11251)	174 (406) 16 (0, 1910)
	Change from baseline Mean (SD) 95% CI	-3787 (1774) -4119, -3455	
Patients with zero factor VIII infusions		0%	34%

[a] Bleeds due to surgery/procedures not included.
[b] Baseline target joints, as assessed by the Investigator, were identified at screening visit.

In study 270-301 for the patients previously enrolled in the non-interventional study, 82% (92/112), 84% (94/112), 75% (82/110), and 74% (81/110) of patients had zero treated bleeds during years 1, 2, 3 and 4, respectively. Seventy-six percent (76%; 85/112), 73% (82/112), 57% (63/110), and 61% (67/110) of patients had zero factor VIII infusions during years 1, 2, 3 and 4, respectively.

In study 270-301 patients (ITT population), ABR for bleeds treated with exogenous factor VIII replacement [median (range): 0 (0, 12.4) bleeds per year] and annualised factor VIII usage [median (range): 0.8 (0, 109.7) infusions per year)] were similar to patients who previously enrolled in the NIS described in Table 9 for the post-factor VIII prophylaxis period following ROCTAVIAN treatment. The median (range) time to discontinuation of prophylactic use of factor VIII concentrates was 4 (0.1, 16.7) weeks, with 130 out of 134 patients discontinuing within 8 weeks.

One-hundred twelve of the 134 patients (84%) remained off prophylaxis post-ROCTAVIAN by end of year 4; twenty-two patients returned to continuous prophylactic use of factor VIII concentrates/other haemostatic agents during this time period. Through the full duration of follow-up, 24 patients at some point returned to continuous prophylactic use of factor VIII concentrates/other haemostatic agents as defined in the study protocol (range: 58, 252 weeks).

Long-term effect

Data on the durability of the treatment are still limited at this stage. At least 4 years of durability data are available in study 270-301, including 15 patients who completed the planned study duration of 5 years. Additionally, 7 years of follow-up data are available from 7 patients receiving the recommended dose of 6×10^{13} vg/kg in study 270-201, and patients continued to show a clinically meaningful response to treatment.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ROCTAVIAN in one or more subsets of the paediatric population in the treatment of haemophilia A (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Valoctocogene roxaparvovec transgene DNA levels (total amount of vector DNA) in various tissues (evaluated in nonclinical studies), blood, and shedding matrices were determined using a quantitative polymerase chain reaction (qPCR) assay. This assay is sensitive to transgene DNA, including fragments of degraded DNA. It does not indicate whether DNA is present in the vector capsid, in cells or in the fluid phase of the matrix (e.g., blood plasma, seminal fluid), or whether intact vector is present. Plasma and semen matrices were further evaluated by measuring encapsidated (potentially infectious) vector DNA using an immunoprecipitation quantitative PCR assay in studies 270-201 and 270-301.

Clinical pharmacokinetics and shedding

Administration of ROCTAVIAN resulted in detectable vector DNA in blood and all shedding matrices evaluated, with peak concentrations observed between 1 and 9 days post-administration. The peak vector DNA concentrations were observed in blood, followed by saliva, semen, stool, and urine. The peak concentration observed to date in blood across studies 270-201 and 270-301 was 2×10^{11} vg/mL. The maximum concentration in any shedding matrix was 1×10^{10} vg/mL. After reaching the maximum in a matrix, the transgene DNA concentration declines steadily.

In the 141 evaluable patients from studies 270-201 and 270-301, encapsidated (potentially infectious) vector DNA was detectable in plasma up to 10 weeks after ROCTAVIAN administration.

In the 140 evaluable patients from studies 270-201 and 270-301, all patients achieved clearance of vector DNA in semen with a maximum time to clearance of 36 weeks. In the 138 evaluable patients from studies 270-201 and 270-301, the maximum time to clearance of encapsidated (potentially infectious) vector DNA in semen was 12 weeks.

In both studies, all patients cleared in urine and saliva, and 126 (89%) patients cleared in stool by the time of the data cut. The maximum time to clearance was 8 weeks for urine, 69 weeks for saliva, and 131 weeks for stool.

Magnitude and duration of shedding appear to be independent of the patient's attained factor VIII activity.

Pharmacokinetics in special populations

No pharmacokinetic studies using valoctocogene roxaparvovec have been conducted in special populations.

5.3 Preclinical safety data

General toxicity

A single intravenous administration of up to 2×10^{14} vg/kg of valoctocogene roxaparvovec in immunocompetent male mice with intact coagulation (CD1 mice), followed by an observation period of up to 26 weeks, showed dose-dependence of plasma levels of the expressed hFVIII-SQ protein and overall factor VIII activity in plasma. Transgene DNA was detected predominantly in spleen and liver, with lower DNA levels still detected at the end of the study (day 182) in lung, mesenteric lymph node, kidney, heart, testis and brain. Vector RNA transcripts were also detected predominantly in the liver with remaining low RNA levels in lung, heart, brain, kidney, lymph nodes, spleen and testis on study end (day 182).

There were no toxicities associated with valoctocogene roxaparvovec in CD1 mice observed for 26 weeks following single doses up to 2×10^{14} vg/kg, except a pattern of haemorrhages, necrosis and fibrosis, occurring primarily in the heart, lungs, epididymis and thymus that was consistent with a coagulopathy likely caused by the formation of antibodies directed against the expressed hFVIII-SQ, which also cross-reacted with the murine factor VIII protein.

In non-GLP studies conducted in non-human primates dosed up to 6×10^{13} vg/kg, an immune response specific for the AAV5 capsid, and an immune response specific to the heterologous hFVIII-SQ protein were observed, associated with transient APTT prolongation in a subset of non-human primates.

Genotoxicity

Vector integration was found following evaluation of liver samples in 12 non-human primates, collected up to 26 weeks following doses up to 6×10^{13} vg/kg of valoctocogene roxaparvovec (which is the corresponding dose level in humans) (see section 4.4 Risk of malignancy as a result of vector integration).

Carcinogenicity

No carcinogenicity study was performed with valoctocogene roxaparvovec.

Reproductive and developmental toxicity

No dedicated reproductive and developmental toxicity studies, including embryo-foetal and fertility assessments, were performed with ROCTAVIAN, as males comprise the majority of the patient population to be treated with ROCTAVIAN. Since hFVIII-SQ DNA has been estimated to persist around/until 67 weeks in testes of CD1 mice after IV injection of a 6×10^{13} vg/kg dose, the potential for vertical transmission to offspring was studied in Rag2-/- mice. There were no instances of germline transmission to pups sired by male mice dosed with valoctocogene roxaparvovec, when assessing liver of F1 pups for hFVIII-SQ DNA by qPCR.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate (E339)
Mannitol (E421)
Poloxamer 188
Sodium chloride
Sodium dihydrogen phosphate dihydrate (E339)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

58 months

Once thawed: chemical and physical in-use stability after thawing has been demonstrated for 10 hours at 25 °C, including hold time in intact vial, preparation time into the syringes, and time for infusion (see section 6.6).

If necessary, an intact vial (stopper not yet punctured) that has been thawed can be stored refrigerated (2 °C to 8 °C) for up to 3 days, upright and protected from light (e.g., in the original carton).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user (see section 6.6).

6.4 Special precautions for storage

Store and transport frozen at ≤ -60 °C. ROCTAVIAN must remain frozen until the patient is ready for treatment to ensure viable product is available for patient administration. Once thawed, do not refreeze.

Store in the original carton in order to protect from light. Store upright.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL vial (cyclic olefin polymer plastic resin) with a stopper (chlorobutyl rubber with fluoropolymer coating), crimp seal (aluminium) and flip-off cap (polypropylene) containing 8 mL of solution for infusion.

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

Each vial is for single use only.

This medicine contains genetically modified organisms (GMOs).

During preparation, administration, and disposal, personal protective equipment (including gown, safety glasses, mask, and gloves) should be worn when handling the valoctocogene roxaparvovec solution and materials that have been in contact with the solution (solid and liquid waste).

ROCTAVIAN must not be exposed to the light of an ultraviolet radiation disinfection lamp.

ROCTAVIAN must be prepared using aseptic technique.

When assembling the infusion system, it must be ensured that the components' surface in contact with the ROCTAVIAN solution consist of the compatible materials listed in Table 10.

Table 10: Compatible infusion system component materials

Component	Compatible materials
Syringes for infusion pump	Polypropylene barrel with a synthetic rubber plunger tip
Syringe cap	Polypropylene
Infusion tubing[a]	Polyethylene
In-line filter	Polyvinylidene fluoride filter with a polyvinyl chloride body
Infusion catheter	Polyurethane based polymer
Stopcocks	Polycarbonate
Needles for extraction from vials	Stainless steel

[a] Tubing extensions should not exceed approximately 100 cm in length.

ROCTAVIAN should be infused using a flow rate-controlled syringe pump.

The following syringes must be prepared:
- Syringes containing ROCTAVIAN (the number of syringes will depend on the patient's dose volume).
- One syringe containing sodium chloride 9 mg/mL (0.9%) solution for injection for infusion line flushing after completion of the ROCTAVIAN infusion.

Infusion requires high-volume, in-line, low protein binding infusion filters with a pore size of 0.22 microns and a maximum operating pressure adequate for the syringe pump or pump settings. Availability of a sufficient number of replacement filters must be ensured, according to the filters' specification for maximum filtered fluid volume.

Thawing and inspection

- ROCTAVIAN must be thawed at room temperature. Do not thaw or warm vials any other way. Thawing time is approximately 2 hours.
- Keep each vial in its carton until ready to thaw. ROCTAVIAN is sensitive to light.
- Remove the required number of vials from their cartons.
- Inspect the vials for damage to the vial or cap. Do not use if damaged.
- Set the vials upright. To achieve optimal thawing, spread them out evenly or place them in racks that have been kept at room temperature.
- Visually confirm that all vials have been thawed. There should be no visible ice. Very gently invert each vial 5 times to mix. It is important to minimise foaming. Let the solution settle for approximately 5 minutes before continuing.
- Then visually inspect the fully thawed vials. Do not use a vial if the solution is not clear, not colourless to pale yellow, or contains visible particles.

For microbiological safety, keep the thawed solution in the vials until it has to be extracted into syringes for infusion.

Time window for further preparation and administration

After thawing, infusion of the solution should be completed within the 10-hour in-use stability limit at 25 °C (see section 6.3). The infusion time depends on infusion volume, rate and patient response and can be, for example, 2 to 5 hours or longer for a patient weighing 100 kg.

Extraction into syringes

Using 18 to 21-gauge sharp needles, slowly extract the entire calculated dose volume of ROCTAVIAN from the vials into the syringes.

Adding the in-line filter and priming the infusion system

- Insert the in-line filter close to the infusion site.
- Prime tubing and filter with ROCTAVIAN.
- When replacing filters during the infusion, use sodium chloride 9 mg/mL (0.9%) solution for injection for priming and flushing.

Administration

- Do not administer this medicinal product before the solution has reached room temperature.
- Infuse the solution through a suitable peripheral vein, using an infusion catheter and a programmable syringe pump.
- Start the infusion at a rate of 1 mL/min. If tolerated, the rate may be increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min (see section 4.2). If clinically indicated for an infusion-related reaction, decrease the rate or stop the infusion and, as necessary, administer

additional medicinal products such as systemic antihistamines, corticosteroids and/or intravenous fluids to manage the infusion reaction or prior to restarting the infusion. When restarting the infusion, start at a rate of 1 mL/min and consider maintaining it at a previously tolerated level for the remainder of the infusion.

- To ensure the patient receives the complete dose, after the volume of the last syringe containing ROCTAVIAN is infused, infuse a sufficient volume of sodium chloride 9 mg/mL (0.9%) solution for injection through the same tubing and filter and at the same infusion rate.
- Maintain venous access during the subsequent observation period (see section 4.4).

Measures to take in case of accidental exposure

All spills of valoctocogene roxaparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and waste that have been in contact with ROCTAVIAN (solid and liquid waste) must be disposed of in compliance with the local guidance for pharmaceutical waste.

7. MARKETING AUTHORISATION HOLDER

BioMarin International Ltd.
Shanbally, Ringaskiddy
County Cork
P43 R298
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1668/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 August 2022
Date of latest renewal: 22 August 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

BioMarin Pharmaceutical Inc.
Novato Campus
46 Galli Drive
Novato, CA 94949
USA

Name and address of the manufacturer(s) responsible for batch release

BioMarin International Ltd.
Shanbally, Ringaskiddy
County Cork
P43 R298
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of ROCTAVIAN in each Member State, the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where ROCTAVIAN is marketed, all healthcare professionals and patients, carers and observers who are expected to prescribe, use or oversee the administration of ROCTAVIAN have access to/are provided with the following educational package. These documents will be translated in the local language to ensure understanding of proposed mitigation measures by physicians and patients:

- Physician Educational Material
- Patient Information Pack

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- The patient guide
- The patient card

The guide for healthcare professionals:

- Patient selection: patients should be selected for treatment with ROCTAVIAN based on the absence of antibodies to AAV5 using an appropriate validated assay and status of liver health based on laboratory and imaging data.
- To inform of the important identified risk of hepatotoxicity and the important potential risks of horizontal and germline transmission, development of factor VIII inhibitors, malignancy in relation to vector genome integration, and thromboembolism, and details on how these risks can be minimised.
- Before a treatment decision is made, the healthcare professional should discuss the risks, benefits, and uncertainties of ROCTAVIAN with the patient when presenting ROCTAVIAN as a treatment option, including:
    - That no predictive factors for no or low responders have been identified. Patients who do not respond are still exposed to long-term risks.
    - That the long-term treatment effect cannot be predicted.
    - That there would be no plans to re-administer the medicinal product for patients who do not respond or have lost the response.
    - Reminding patients about the importance to enrol in a registry for follow up of long-term effects.
    - That ROCTAVIAN use will require in most cases co-administration of corticosteroids to manage the liver damage that this medicinal product might induce. This requires adequate monitoring of patients and careful consideration of other co-medications, to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of ROCTAVIAN.

The patient information pack should contain:

- The patient information leaflet
- The patient guide
- The patient card

The patient guide:

- Importance to fully understand the benefits and risks of ROCTAVIAN treatment, what is known and not yet known about the long-term effects, related to both safety and efficacy.
- Therefore, before a decision is made about starting on the therapy the doctor will discuss with the patient the following:

- That not all patients may benefit from treatment with ROCTAVIAN and the reasons for this have not been established. Patients not responding to treatment will still be exposed to long-term risks.
- That ROCTAVIAN will, in most cases, require co-treatment with corticosteroids to overcome the liver damage that this medicine may produce, and that the doctor will ensure that patients are available for regular blood tests to check response to ROCTAVIAN and assess liver health. Patients should inform the healthcare professional about current use of corticosteroids or other immunosuppressants. If the patient cannot take corticosteroids, the doctor may recommend alternative medicines to manage problems with the liver.
- That ROCTAVIAN has a viral vector component, and it may be associated with an increased risk of malignant tumour.
- Details how the important identified risk of hepatotoxicity and the important potential risks of horizontal and germline transmission, development of factor VIII inhibitors, malignancy in relation to vector genome integration, and thromboembolism can be recognised and minimised by regular monitoring as recommended by doctors.
- That the patient will get a patient card that should be shown to any doctor or a nurse whenever the patient has a medical appointment.
- The importance to participate in the patients' registry for long-term surveillance of 15 years.

The patient card:

- This card is to inform healthcare professionals that the patient has received ROCTAVIAN for haemophilia A.
- The patient should show the patient card to a doctor or a nurse whenever they have an appointment.
- The card should mention the specific mitigation measures to minimise the risks related to hepatotoxicity, horizontal and germline transmission, development of factor VIII inhibitors, malignancy in relation to vector genome integration, and thromboembolism.
- The card should warn healthcare professionals that the patient is likely undergoing treatment with corticosteroids for minimising the risk of hepatotoxicity with ROCTAVIAN.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
In order to further characterise the long-term efficacy and safety of ROCTAVIAN in adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to AAV5, the MAH should conduct and submit the final results of study 270-401, a follow-up study of patients enrolled in the clinical studies.	31 July 2038
In order to further characterise the long-term efficacy and safety of ROCTAVIAN in adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to AAV5, the MAH should conduct and submit the final results of the study 270-801, a Retrospective Cohort Study of patients treated with valoctocogene roxaparvovec based on data from a registry, according to an agreed protocol.	30 June 2044

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of ROCTAVIAN in adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to AAV5, the MAH should submit the final results including 5 years follow-up of the phase 3, single arm study 270-301.	28 February 2026
In order to confirm the efficacy and safety of ROCTAVIAN, adequate corticosteroid regimen and to identify predictive factors for no or low response in adults with severe haemophilia A (congenital factor VIII deficiency), the MAH should submit the final results of the phase 3 single arm study 270-303 in patients receiving a prophylactic corticosteroid regimen. Interim data from open-label studies 270-203 and 270-205 should also be provided.	28 February 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

ROCTAVIAN 2×10^{13} vector genomes/mL solution for infusion
valoctocogene roxaparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 16×10^{13} vector genomes of valoctocogene roxaparvovec in 8 mL solution.

3. LIST OF EXCIPIENTS

Excipients: E339, E421, poloxamer 188, sodium chloride, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen at ≤ -60 °C.
Store in the original carton in order to protect from light.
Store upright.

Once thawed, do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms.
Dispose of in compliance with the local guidance for pharmaceutical waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Ltd.
Shanbally, Ringaskiddy, County Cork
P43 R298, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1668/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ROCTAVIAN 2×10^{13} vector genomes/mL solution for infusion
valoctocogene roxaparvovec
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ROCTAVIAN 2 × 10^{13} vector genomes/mL solution for infusion
valoctocogene roxaparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.

What is in this leaflet

1. What ROCTAVIAN is and what it is used for

What ROCTAVIAN is
ROCTAVIAN is a gene therapy product that contains the active substance valoctocogene roxaparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic deficiency.

What ROCTAVIAN is used for
This medicine is used for the treatment of severe haemophilia A in adults who do not have current or past inhibitors to factor VIII and who do not have antibodies to the virus vector AAV5.

Haemophilia A is a condition where people inherit an altered form of a gene needed to make factor VIII, an essential protein required for blood to clot and stop any bleeding. People with haemophilia A cannot produce factor VIII and are prone to internal or external bleeding episodes.

How does ROCTAVIAN work
The active substance in ROCTAVIAN is based on a virus which does not cause disease in humans. This virus has been modified so that it cannot spread in the body but can deliver a working copy of the factor VIII gene into liver cells. This enables liver cells to produce factor VIII protein and raise levels of working factor VIII in the blood. In turn, this helps the blood to clot more normally and prevents bleeding or reduces bleeding episodes.

2. What you need to know before you are given ROCTAVIAN

You will not be given ROCTAVIAN
- if you are allergic to valoctocogene roxaparvovec or any of the other ingredients of this medicine (listed in section 6).

- if you have an active infection or if you have a chronic (long-term) infection that is not controlled by medicines you take, or if you have scarring of the liver (significant liver fibrosis or cirrhosis), as this could affect your body's initial response to ROCTAVIAN.
- if you have antibodies to the type of virus used to make this medicine. Your doctor will test you beforehand to see if this is the case.

If any of the above applies to you, or if you are unsure of any of the above, please talk to your doctor before you receive ROCTAVIAN.

Warnings and precautions

Importance of liver health
- Your liver is the organ that produces factor VIII after treatment with ROCTAVIAN. You should take care of your liver's health so that it is functioning as optimally as possible and you can produce factor VIII and continue to produce factor VIII on an ongoing basis.
- Talk to your doctor about what you can do to improve and maintain your liver's health (see also **You will not be given ROCTAVIAN**, above, and **Other medicines and ROCTAVIAN** and **ROCTAVIAN with alcohol**, below).
- Your doctor may advise you against treatment with ROCTAVIAN if you have a liver disease that may prevent ROCTAVIAN from working well.

You may need to take an additional medicine
- You may need to take another medicine (corticosteroids) for an extended period of time (2 months or longer) after being given ROCTAVIAN to manage problems with your liver seen in tests. Corticosteroids may cause side effects while you receive them. Your doctor may advise you to avoid or postpone treatment with ROCTAVIAN if you are not able to safely receive corticosteroids and may also advise you of steps you should take for safe use or may give you an alternative medicine. See also section 3.

Side effects during or shortly after ROCTAVIAN infusion
- Infusion-related side effects can occur during or shortly after you are given the ROCTAVIAN infusion (drip). Symptoms of such side effects are listed in **section 4. Possible side effects**. Tell your doctor or nurse **immediately** if you experience these or any other symptoms during or shortly after the infusion. Depending on your symptoms, your infusion may be slowed down or temporarily stopped, or you may be given medicines to treat them. Before you are discharged, your doctor will provide you with information on what to do in case you experience new side effects or side effects which come back once you leave the medical facility.

Possibility of unwanted blood clots when factor VIII levels improve
- After treatment with ROCTAVIAN, your factor VIII protein level may increase. In some patients, it may increase to levels above the normal range for a period of time.

  Factor VIII is the protein necessary to form stable clots in your blood. Depending on your individual risk factors, an improvement in factor VIII levels may mean an increased possibility of unwanted blood clots (so called "thromboses", in either veins or arteries). Discuss with your doctor your general risk factors for unwanted clots and for cardiovascular disease, and what to do about them. Also ask how to recognise symptoms of unwanted clots and what to do if you think you may have one.

Avoiding blood donations and donations for transplantations
- Do not donate blood, organs, tissues, or cells for transplant.

Immunocompromised patients or patients receiving immunosuppressive treatment
- If you are immunocompromised (when your immune system's ability to fight infections is reduced) or receiving immunosuppressive treatment, contact your doctor before starting treatment with ROCTAVIAN. You may need to be monitored more closely if your immune

system is not working properly to ensure you can receive treatment and other medicines such as corticosteroids or if you need to change your existing medicines.

Receiving gene therapy again in the future

- After receiving ROCTAVIAN, your immune system will produce antibodies to the shell of the AAV vector. It is not yet known whether or under which conditions therapy with ROCTAVIAN may be repeated. It is also not yet known whether or under which conditions subsequent use of another gene therapy may be possible.

Use of other haemophilia treatments

- After ROCTAVIAN use, talk to your doctor about if or when you should stop your other haemophilia treatments and develop a treatment plan of what to do in case of surgery, trauma, bleeds, or any procedures that could potentially increase the risk of bleeding. It is very important to continue your monitoring and doctor visits to determine if you need to take other treatments to manage haemophilia.

Monitoring tests

Before treatment with ROCTAVIAN, your doctor will perform tests to assess your liver health.

After treatment with ROCTAVIAN blood tests will be done to check:

- when your liver starts producing factor VIII so you know when you can stop your regular treatment with factor VIII products,
- how much factor VIII your liver produces on an ongoing basis,
- how your liver cells react to the treatment with ROCTAVIAN, and
- whether you develop inhibitors (neutralising antibodies) to factor VIII.

How often blood tests have to be done depends on how you react to ROCTAVIAN. In general, during the first 26 weeks after treatment, blood tests will be done every week, then every 2 to 4 weeks until the end of the first year. After the first year, blood tests will be done less frequently as advised by your doctor. **It is important that you discuss the schedule for these blood tests with your doctor so that they can be carried out as necessary.**

Because not all patients will respond to ROCTAVIAN and the reasons for this have not been established, your doctor will not be able to predict whether you will respond fully to the treatment. There is the potential that you may not benefit from ROCTAVIAN while still be exposed to long-term risks.

If you respond to the treatment, it is unknown how long the treatment will last. A positive treatment effect of up to five years has been reported in some patients.

There are no plans to administer the medicine a second time for patients who do not respond or have lost the response.

Long-term follow-up tests may be required to verify a continued safe and effective response to ROCTAVIAN.

Risk of malignancy potentially associated with ROCTAVIAN

- ROCTAVIAN can insert into liver cell DNA and there is the possibility that it can also insert into DNA of other body cells. As a consequence, ROCTAVIAN could contribute to a risk of cancer. Although there is no evidence of this in the clinical trials so far, this remains possible because of the nature of the medicine. You should therefore discuss this with your physician. After treatment with ROCTAVIAN, you will be recommended to enrol in a registry to help study the long-term safety of the treatment for 15 years, how well it continues to work and any side effects that may be linked to the treatment. In the event of cancer, your doctor may take a sample for further evaluation.

Children and adolescents
ROCTAVIAN is for use in adults only. ROCTAVIAN has not yet been tested for use in children or adolescents.

Other medicines and ROCTAVIAN
Before and after treatment with ROCTAVIAN, tell your doctor if you are using, have recently used or plan to use any other medicines, including herbal products or nutritional supplements. This is to make sure you avoid, as far as possible, taking anything that could damage your liver or impact the response to corticosteroids or ROCTAVIAN (such as isotretinoin, a medicine which is used to treat acne) or some medicines for the treatment of HIV (see section above on Immunocompromised patients or patients receiving immunosuppressive treatment). This is especially important during the first year after ROCTAVIAN treatment (see also **Warnings and precautions**).

As corticosteroids can affect the body's immune (defence) system, your doctor may adjust the timing of vaccinations and may recommend you do not receive certain vaccinations while on corticosteroid treatment. Talk to your doctor if you have any questions.

ROCTAVIAN with alcohol
Drinking alcohol could affect your liver's ability to produce factor VIII after treatment with ROCTAVIAN. You should avoid alcohol for at least one year after treatment. Talk to your doctor about how much alcohol may be acceptable for you after the first year (see also **Warnings and precautions**).

Pregnancy, breast-feeding and fertility
ROCTAVIAN is not recommended in women who are able to become pregnant. It is not yet known whether ROCTAVIAN can be used safely in these patients as the effects on pregnancy and the unborn child are not known. It is also not known whether ROCTAVIAN passes into breast milk.

There is no information on the effect of ROCTAVIAN on male or female fertility.

Use of contraception and avoiding partner pregnancy for a period of time
- After a male patient has been treated with ROCTAVIAN, the patient and any female partner must avoid pregnancy for **6 months.** You should use effective contraception (e.g., double-barrier contraception such as condom and diaphragm). This is to prevent the theoretical risk that the factor VIII gene from a father's ROCTAVIAN treatment is transmitted to a child with unknown consequences. For the same reason, male patients must not donate semen for 6 months. Discuss with your doctor which methods of contraception are suitable.

Driving and using machines
Temporary light-headedness (near-fainting), dizziness, tiredness, and headaches were observed after ROCTAVIAN infusion. If you are affected, you should use caution until you are certain that ROCTAVIAN does not adversely affect your ability to drive or use machines. Talk to your doctor about this.

ROCTAVIAN contains sodium
This medicine contains 29 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.5% of the recommended maximum daily dietary intake of sodium for an adult. The amount of sodium you will receive depends on the number of ROCTAVIAN vials used for your infusion.

3. How ROCTAVIAN is given

ROCTAVIAN will be given by a doctor who specialises in the management of your condition.

The doctor will work out the correct dose for you, based on your body weight.

Treatment with ROCTAVIAN consists of **one single infusion (drip) into a vein**. The infusion may take several hours to be completed.

The infusion will be given to you in a medical facility. During and after the infusion, you will be observed to detect possible side effects.

You will be allowed to go home (usually later the same day) once it has been decided that further observation is not necessary.

Additional medicine you may need

You may need to take another medicine (corticosteroids) for an extended period of time (for example, 2 months or longer) after ROCTAVIAN treatment to improve your response to therapy. It is important that you take this additional medicine according to the instructions given. You should read the package leaflet for any additional medicine you are prescribed and discuss with your doctor the possible side effects and any monitoring that may be needed.

If you are given more ROCTAVIAN than you should be
As this medicine is given in hospital, and the dose is worked out and checked by your medical team, it is unlikely that you will be given too much. If you are given too much ROCTAVIAN, you might have higher factor VIII levels than needed, which may theoretically increase the possibility of unwanted blood clots. If this occurs, your doctor will treat you as necessary.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related side effects can occur during or shortly after your infusion (commonly; may affect up to 1 in 10 people). Tell your doctor or nurse **immediately** if you experience any of the following symptoms or any other symptoms during or shortly after the infusion:
- Hives or other rashes, itching
- Difficulty breathing, sneezing, coughing, runny nose, watery eyes, tingling throat
- Nausea (feeling sick), diarrhoea
- High or low blood pressure, rapid heartbeat, light-headedness (near-fainting)
- Muscle pain, back pain
- Fever, chills, shivering

Such symptoms can occur alone or in combination. Depending on your symptoms, your infusion may be slowed down or temporarily stopped, or you may be given medicines to treat them. Before discharging you, your doctor will provide you with information on what to do in case you experience a new or recurring side effect once you leave the medical facility.

Increased levels of liver proteins occurred after ROCTAVIAN infusion. In some cases, these increases occurred together with a decrease in factor VIII levels. Increases in the levels of liver proteins seen in blood tests can be the reason to start treatment with a corticosteroid.

The following side effects may happen with ROCTAVIAN. Some of these side effects can occur during or shortly after infusion.

Very common (may affect more than 1 in 10 people)
- Increased levels of liver proteins seen in blood tests
- Nausea (feeling sick)
- Headache

- Factor VIII above normal levels
- Tiredness
- Diarrhoea
- Abdominal (belly) pain
- Vomiting
- Increased levels of creatine phosphokinase (CPK) protein (an enzyme released into the blood when muscle is damaged) seen in blood tests

Common (may affect up to 1 in 10 people)
- Rash (including hives or other forms of rash)
- Heartburn (dyspepsia)
- Muscle pain
- Flu-like symptoms
- Dizziness
- Itching
- Increased blood pressure
- Allergic reaction

Uncommon (may affect up to 1 in 100 people)
- Light-headedness (near-fainting)
- Difficulty breathing

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How ROCTAVIAN is stored

Keep this medicine out of the sight and reach of children.

This medicine must not be used after the expiry date which is stated on the carton and vial after "EXP". The expiry date refers to the last day of that month.

ROCTAVIAN will be stored by the healthcare professionals at your healthcare facility. It must be stored upright and in its original carton (in order to protect it from light).

It must be stored and transported frozen at or below -60 °C. Once thawed, it must be used within 10 hours at 25 °C (this includes hold time in the vial and syringe, and time for infusion) or discarded. If needed, an intact vial (stopper not yet punctured) that has been thawed can be stored refrigerated (2 to 8 °C) for up to 3 days, upright and protected from light (e.g., in the original carton).

Thawed ROCTAVIAN must not be used if the solution is not clear and colourless to pale yellow.

6. Contents of the pack and other information

What ROCTAVIAN contains
- The active substance is valoctocogene roxaparvovec.
- The other ingredients are; disodium phosphate dodecahydrate (E339), mannitol (E421), poloxamer 188, sodium chloride, sodium dihydrogen phosphate dihydrate (E339), and water for injections.
  See end of **section 2 ROCTAVIAN contains sodium** for information on the total sodium content.

This medicine contains genetically modified organisms (GMOs).

What ROCTAVIAN looks like and contents of the pack
When thawed, ROCTAVIAN is a clear, colourless to pale yellow solution for infusion. It is supplied in a vial.

Pack size: 1 vial of 8 mL

Marketing Authorisation Holder and Manufacturer
BioMarin International Ltd.
Shanbally, Ringaskiddy
County Cork
P43 R298
Ireland

This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using ROCTAVIAN.

Precautions to be taken before handling or administering the medicinal product

Each vial is for single use only.

This medicine contains genetically modified organisms (GMOs).

During preparation, administration, and disposal, personal protective equipment (including gown, safety glasses, mask, and gloves) should be worn when handling the valoctocogene roxaparvovec solution and materials that have been in contact with the solution (solid and liquid waste).

ROCTAVIAN must not be exposed to the light of an ultraviolet radiation disinfection lamp.
ROCTAVIAN must be prepared using aseptic technique.

When assembling the infusion system, it must be ensured that the components' surface in contact with the ROCTAVIAN solution consist of the compatible materials listed in the SmPC.

Compatible infusion system component materials

Component	Compatible materials
Syringes for infusion pump	Polypropylene barrel with a synthetic rubber plunger tip
Syringe cap	Polypropylene
Infusion tubing[a]	Polyethylene
In-line filter	Polyvinylidene fluoride filter with a polyvinyl chloride body
Infusion catheter	Polyurethane based polymer
Stopcocks	Polycarbonate
Needles for extraction from vials	Stainless steel

[a] Tubing extensions should not exceed approximately 100 cm in length

ROCTAVIAN is to be infused using a flow rate-controlled syringe pump.

The following syringes must be prepared:
- Syringes containing ROCTAVIAN (the number of syringes will depend on the patient's dose volume).
- One syringe containing sodium chloride 9 mg/mL (0.9%) solution for injection for infusion line flushing after completion of the ROCTAVIAN infusion.

Infusion requires high volume, inline, low protein binding infusion filters with a pore size of 0.22 microns and a maximum operating pressure adequate for the syringe pump or pump settings. Availability of a sufficient number of replacement filters must be ensured, according to the filters' specification for maximum filtered fluid volume.

Thawing and inspection

- ROCTAVIAN must be thawed at room temperature. Do not thaw or warm vials any other way. Thawing time is approximately 2 hours.
- Keep each vial in its carton until ready to thaw. ROCTAVIAN is sensitive to light.
- Remove the required number of vials from their cartons.
- Inspect the vials for damage to the vial or cap. Do not use if damaged.
- Set the vials upright. To achieve optimal thawing, spread them out evenly or place them in racks that have been kept at room temperature.
- Visually confirm that all vials have been thawed. There should be no visible ice. Very gently invert each vial 5 times to mix. It is important to minimise foaming. Let the solution settle for approximately 5 minutes before continuing.
- Then visually inspect the fully thawed vials. Do not use a vial if the solution is not clear, not colourless to pale yellow, or contains visible particles.

For microbiological safety, keep the thawed solution in the vials until it has to be extracted into syringes for infusion.

Time window for further preparation and administration

After thawing, infusion of the solution should be completed within the 10-hour in-use stability limit at 25 °C. The infusion time depends on infusion volume, rate and patient response and can be, for example, 2 to 5 hours or longer for a patient weighing 100 kg.

Extraction into syringes

Using 18 to 21-gauge sharp needles, slowly extract the entire calculated dose volume of ROCTAVIAN from the vials into the syringes.

Adding the in-line filter and priming the infusion system

- Insert the in-line filter close to the infusion site.
- Prime tubing and filter with ROCTAVIAN.
- When replacing filters during the infusion, use sodium chloride 9 mg/mL (0.9%) solution for injection for priming and flushing.

Administration

- Do not administer this medicinal product before the solution has reached room temperature.
- Infuse the solution through a suitable peripheral vein, using an infusion catheter and a programmable syringe pump.
- Start the infusion at a rate of 1 mL/min. If tolerated, the rate may be increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min. If clinically indicated for an infusion-related reaction, decrease the rate or stop the infusion and, as necessary, administer additional medicinal products such as systemic antihistamines, corticosteroids and/or intravenous fluids to manage the infusion reaction or prior to restarting the infusion. When restarting the infusion, start at a rate of 1 mL/min and consider maintaining it at a previously tolerated level for the remainder of the infusion.
- To ensure the patient receives the complete dose, after the volume of the last syringe containing ROCTAVIAN is infused, infuse a sufficient volume of sodium chloride 9 mg/mL (0.9%) solution for injection through the same tubing and filter and at the same infusion rate.
- Maintain venous access during the subsequent observation period.

Measures to take in case of accidental exposure

All spills of valoctocogene roxaparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and waste that have been in contact with ROCTAVIAN (solid and liquid waste) must be disposed of in compliance with the local guidance for pharmaceutical waste.