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

Adakveo 10 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 10 mg crizanlizumab.

One vial of 10 ml contains 100 mg crizanlizumab.

Crizanlizumab is a monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Colourless to slightly brownish-yellow liquid at pH 6 and with an osmolality of 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the management of sickle cell disease.

Posology

Recommended dose
The recommended dose of crizanlizumab is 5 mg/kg administered over a period of 30 minutes by intravenous infusion at week 0, week 2, and every 4 weeks thereafter.

Crizanlizumab can be given alone or with HU/HC.

Delayed or missed doses
If a dose is missed, the treatment should be administered as soon as possible.
- If crizanlizumab is administered within 2 weeks after the missed dose, dosing should be continued according to the patient's original schedule.
- If crizanlizumab is administered more than 2 weeks after the missed dose, dosing should be continued every 4 weeks thereafter.

Management of infusion-related reactions
Table 1 summarises the recommendations for the management of infusion-related reactions (see also sections 4.4 and 4.8).

Table 1 Recommendations for managing infusion-related reactions

Severity of adverse reaction	Management recommendation
Mild (Grade 1) to moderate (Grade 2) infusion-related reactions	Temporarily interrupt or reduce the infusion rate. Initiate symptomatic treatment.* For subsequent infusions, consider premedication and/or slower infusion rate.
Severe (≥ Grade 3) infusion-related reactions	Discontinue treatment with Adakveo. Initiate symptomatic treatment.*
* E.g. antipyretic, analgesic and/or antihistamine. Caution should be exercised with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g. treatment of anaphylaxis).	

Special populations
Elderly
Crizanlizumab has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of crizanlizumab in adults are not affected by age.

Renal impairment
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
The safety and efficacy of crizanlizumab in patients with hepatic impairment have not been established. Crizanlizumab is a monoclonal antibody and is cleared via catabolism (i.e. breakdown into peptides and amino acids), and a change in dose is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of crizanlizumab in paediatric patients from 6 months to 16 years have not been established. No data are available.

There is no relevant use of crizanlizumab in infants aged less than 6 months for the indication of prevention of recurrent vaso-occlusive crises.

Method of administration

Adakveo should be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 5% before administration.

The diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter by intravenous infusion over a period of 30 minutes. It must not be administered by intravenous push or bolus.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to Chinese Hamster Ovary (CHO) cell products.

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.

Infusion-related reactions

In clinical studies, infusion-related reactions (defined as occurring during infusion or within 24 hours of the infusion) were observed in 3 patients (2.7%) treated with crizanlizumab 5 mg/kg (see section 4.8).

In the post-marketing setting, cases of infusion-related reactions were reported, including severe pain events, differing in location, severity, and/or nature from patient's baseline and requiring hospitalisation in several cases. The majority of these infusion-related reactions occurred during infusion or within a few hours of the completion of the first or second infusion. However, later onset of severe pain events has also been reported, following previous well-tolerated infusions. Some patients have also experienced subsequent complications such as acute chest syndrome and fat embolism, particularly those treated with steroids.

Patients should be monitored for, and advised of, signs and symptoms of infusion-related reactions, which may include pain in various locations, headache, fever, chills, nausea, vomiting, diarrhoea, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing (see section 4.8).

In the event of a severe infusion-related reaction, crizanlizumab should be discontinued and appropriate therapy should be instituted (see section 4.2).

For recommendations on managing mild or moderate infusion-related reactions see section 4.2.

Caution should be exercised with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g. treatment of anaphylaxis).

Laboratory test interference: automated platelet counts

Interference with automated platelet counts (platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when tubes containing EDTA (ethylenediaminetetraacetic acid) were used. This may lead to unevaluable or falsely decreased platelet counts. There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect *in vivo*.

To mitigate the potential for laboratory test interference, it is recommended to run the test as soon as possible (within 4 hours of blood collection) or use citrate tubes. When needed, platelet counts can be estimated via a peripheral blood smear.

Excipients with known effect

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies.

Monoclonal antibodies are not metabolised by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are substrates, inhibitors or inducers of CYP450 are not expected to affect the pharmacokinetics of crizanlizumab. In clinical studies, HU/HC had no effect on crizanlizumab pharmacokinetics in patients.

No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of Adakveo in pregnant women. Based on data from animal studies, crizanlizumab has the potential to cause foetal losses when administered to a pregnant woman (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Adakveo during pregnancy and in woman of childbearing potential not using contraception.

To help determine the effects in pregnant women, healthcare professionals are encouraged to report all pregnancy cases and complications during pregnancy (from 105 days prior to the last menstrual period onward) to the local representative of the marketing authorisation holder (see package leaflet), in order to allow monitoring of these patients through the PRegnancy outcomes Intensive Monitoring programme (PRIM). In addition, all adverse pregnancy events should be reported via the national reporting system listed in Appendix V.

Breast-feeding

It is unknown whether crizanlizumab is excreted in human milk after administration of Adakveo. There are no data on the effects of crizanlizumab on the breast-fed newborn/infant or on milk production.

Because many medicinal products, including antibodies, can be excreted in human milk, a risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue Adakveo therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of Adakveo on human fertility. Available non-clinical data do not suggest an effect on fertility under crizanlizumab treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Adakveo may have a minor influence on the ability to drive and use machines. Dizziness, fatigue and somnolence may occur following administration of crizanlizumab.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (≥10% of patients) in the Adakveo 5 mg/kg group were arthralgia, nausea, back pain, pyrexia and abdominal pain. These adverse drug reactions, along with myalgia, musculoskeletal chest pain and diarrhoea, may be signs and symptoms of an infusion-related reaction when observed during infusion or within 24 hours of an infusion (see section 4.4). Severe events were observed for pyrexia and arthralgia (each 0.9%). Severe pain events as part of infusion-related reactions were reported post-marketing.

Tabulated list of adverse reactions

Table 2 lists adverse reactions based on pooled data from two studies: the pivotal study, SUSTAIN, and a single-arm, open-label pharmacokinetics/pharmacodynamics and safety study. Use of crizanlizumab in combination with HU/HC did not result in any meaningful differences in the safety profile. Adverse reactions reported in the post-marketing setting are also presented in table 2.

Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: 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 2 Adverse reactions from clinical studies and post-marketing surveillance

System organ class	**Frequency**	**Adverse reaction**
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Very common	Nausea, abdominal pain*
	Common	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus*
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, back pain
	Common	Myalgia, musculoskeletal chest pain
General disorders and administration site conditions	Very common	Pyrexia
	Common	Infusion site reaction*
	Not known	Pain[#]
Injury, poisoning and procedural complications	Common	Infusion-related reaction

*The following groupings contain the following MedDRA preferred terms:
- Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness
- Pruritus: pruritus and vulvovaginal pruritus
- Infusion site reaction: infusion site extravasation, infusion site pain, and infusion site swelling

[#] Pain in various locations occurring during infusion or within 24 hours of the infusion (e.g. potential infusion related reaction). This includes but is not limited to abdominal pain, arthralgia, back pain, bone pain, chest pain, general body pain, headache, muscle spasms, musculoskeletal pain, myalgia, pain in extremity. See section 4.4.

Description of selected adverse reactions

Immunogenicity
In clinical studies, treatment-induced anti-crizanlizumab antibodies were transiently detected in 1 patient (0.9%) among the 111 patients who received Adakveo 5 mg/kg.

There was no evidence of altered pharmacokinetics or of an altered safety profile with anti-crizanlizumab antibody development.

Paediatric population

Frequency, type and severity of adverse reactions in patients aged 16 and 17 years are expected to be the same as in adults. The safety of crizanlizumab was evaluated in 3 patients aged <18 years.

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

No cases of overdose have been reported in clinical studies.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, ATC code: B06AX01

Mechanism of action

Crizanlizumab is a selective IgG2 kappa humanised monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks the interaction with its ligands, including P-selectin glycoprotein ligand 1. Crizanlizumab can also dissociate preformed P-selectin/PSGL-1 complex. P-selectin is an adhesion molecule expressed on activated endothelial cells and platelets. It plays an essential role in the initial recruitment of leukocytes and the aggregation of platelets to the site of vascular injury during inflammation. In the chronic pro-inflammatory state associated with sickle cell disease, P-selectin is over-expressed and circulating blood cells and the endothelium are activated and become hyperadhesive. P-selectin-mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and vaso-occlusive crises (VOC). Elevated levels of P-selectin are found in patients with sickle cell disease.

Binding P-selectin on the surface of the activated endothelium and platelets has been shown to effectively block interactions between endothelial cells, platelets, red blood cells and leukocytes, thereby preventing vaso-occlusion.

Pharmacodynamic effects

Throughout clinical studies, treatment with crizanlizumab 5 mg/kg resulted in dose-dependent, immediate and sustained P-selectin inhibition (as measured *ex vivo*) in patients with sickle cell disease.

Clinical efficacy and safety

The efficacy of crizanlizumab, with or without HU/HC, was evaluated in the pivotal study SUSTAIN, a 52-week, randomised, placebo-controlled, double-blind, multicentre clinical study in sickle cell disease patients with a history of vaso-occlusive crises (VOCs).

In this study, VOCs were defined as those leading to a healthcare visit, which captured all acute episodes of pain with no other cause than a vaso-occlusive event that required a healthcare visit and treatment with oral or parenteral opioids or parenteral non-steroidal anti-inflammatory drugs (NSAIDs). Acute chest syndrome, hepatic sequestration, splenic sequestration and priapism (requiring a healthcare visit), by definition, were also considered VOCs.

A total of 198 sickle cell disease patients aged 16 to 63 years (inclusive; mean age 30.1±10.3 years), with any sickle cell disease genotype (including HbSS [71.2%], HbSC [16.2%], HbSbeta0-thalassaemia [6.1%], HbSbeta+-thalassaemia [5.1%], and others [1.5%]) and a history of between 2 and 10 VOCs in the previous 12 months (62.6% and 37.4% of the patients had 2-4 or 5-10 VOCs, respectively), were randomised 1:1:1 to Adakveo 5 mg/kg, Adakveo 2.5 mg/kg or placebo. The majority of patients were Black or African American (91.9%). Patients received Adakveo with (62.1%) or without (37.9%) HU/HC. Randomisation was stratified by patients already receiving HU/HC (Y/N) and by number of VOCs in the previous 12 months (2 to 4, 5 to 10). Patients were allowed to take medicinal products to relieve pain (i.e. paracetamol, NSAIDs and opioids) and to receive occasional transfusions on an "as needed" basis. Patients participating in a chronic transfusion programme (pre-planned series of transfusions for prophylactic purposes) were excluded from the study.

Treatment with Adakveo 5 mg/kg resulted in a 45.3% lower median annual rate of VOCs compared to placebo (Hodges-Lehmann, median absolute difference of -1.01 compared with placebo, 95% CI [-2.00, 0.00]), which was statistically significant (p=0.010). The median annual rates of uncomplicated VOCs (any VOCs as defined above, excluding acute chest syndrome, hepatic sequestration, splenic sequestration or priapism) and days hospitalised were 62.9% and 41.8% lower in the Adakveo 5 mg/kg than in the placebo group, respectively. The VOCs occurring during the study were assessed by an independent review committee.

Main efficacy outcomes of the pivotal SUSTAIN study are summarised in Tables 3 and 4.

Table 3 Results from SUSTAIN clinical study in sickle cell disease

Event	**Adakveo 5 mg/kg (N=67)** (standard median)	**Placebo (N=65)** (standard median)	**Change vs placebo**	**Hodges-Lehmann median difference** (95% CI)	**p-value** (Wilcoxon rank sum)
Primary endpoint Annual rate of VOCs	1.63	2.98	-45.3%	-1.01 (-2.00, 0.00)	0.010
Secondary endpoints					
Annual rate of days hospitalised	4.00	6.87	-41.8%	0.00 (-4.36, 0.00)	0.450
Annual rate of uncomplicated VOCs	1.08	2.91	-62.9%	-1.00 (-1.98, 0.00)	-

The primary (annual rate of VOC leading to healthcare visit) and key secondary (annual rate of days hospitalised) endpoints were the only ones formally tested for statistical significance according to protocol.

The clinical effect demonstrated in the primary efficacy analysis was supported by multiple supplementary analyses including a negative binomial regression on investigator assessments with a conservative method to handle missing data due to early discontinuation of treatment based on outcomes in the placebo group (RR=0.74, 95% CI=0.52, 1.06).

In the Adakveo 5 mg/kg group, clinically significant reductions in the annual rate of VOCs were observed across important subgroups (HU/HC use, 2-4 or 5-10 VOCs in the previous 12 months, and HbSS or non-HbSS genotypes; see Table 4).

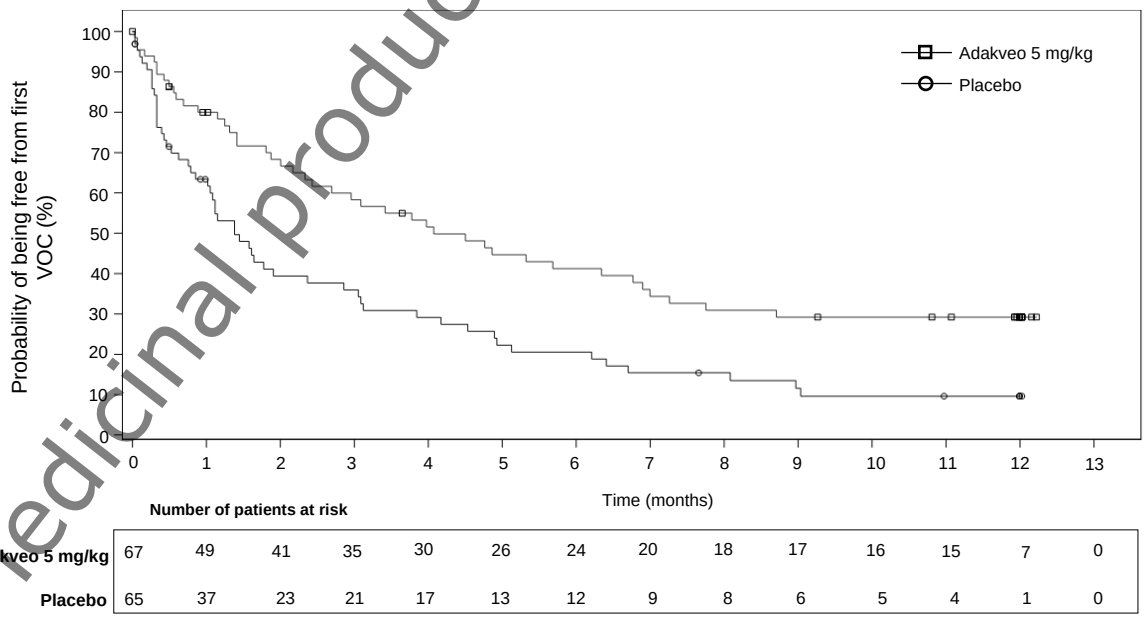
Table 4 Annual rate of VOCs in patients - subgroup analyses

Subgroup		**Adakveo 5 mg/kg (N=67)** (standard median)	**Placebo (N=65)** (standard median)	**Change vs placebo**	**Hodges-Lehmann median difference (95% CI)**
HU/HC use	Yes	n=42 2.43	n= 40 3.58	-32.1%	-1.01 (-2.44, 0.00)
	No	n=25 1.00	n=25 2.00	-50.0%	-1.02 (-2.00, 0.00)
Number of VOCs in previous 12 months	2-4 VOCs	n=42 1.14	n=41 2.00	-43.0%	-0.05 (-1.56, 0.01)
	5-10 VOCs	n=25 1.97	n=24 5.32	-63.0%	-2.74 (-5.00, -0.83)
Sickle cell disease genotypes, including HbSC	HbSS	n=47 1.97	n=47 3.01	-34.6%	-1.01 (-2.18, 0.00)
	Non-HbSS	n=20 0.99	n=18 2.00	-50.5%	-1.01 (-2.01, 0.00)

A greater than two-fold increase in the proportion of patients with no VOC and who completed the study was observed in the Adakveo 5 mg/kg group compared to placebo (22% vs 8%; odds ratio [95% CI]: 3.57 [1.20, 10.63]). A similar difference was also observed across important subgroups (HU/HC use, genotype).

Treatment with Adakveo 5 mg/kg was also associated with a three-fold longer Kaplan-Meier estimated median time to first VOC compared with placebo (4.07 vs 1.38 months; HR=0.495, 95% CI: 0.331, 0.741) (Figure 1) and a two-fold longer median time from randomisation to second VOC compared to placebo (10.32 vs 5.09 months; HR=0.534, 95% CI: 0.329, 0.866).

Figure 1 Kaplan-Meier curve of time to first VOC



Paediatric population

The efficacy of crizanlizumab in patients aged 16 and 17 years is expected to be the same as in adults. Three patients (2.7%) aged less than 18 years were treated with crizanlizumab 5 mg/kg in clinical studies.

The European Medicines Agency has deferred the obligation to submit the results of studies with Adakveo in one or more subsets of the paediatric population in the treatment of sickle cell disease (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

Absorption

The median time to reach maximum serum concentration of crizanlizumab (T_{max}) was 1.92 hours at steady state following intravenous administration of 5 mg/kg over a period of 30 minutes in sickle cell disease patients.

Distribution

Crizanlizumab distribution is typical of endogenous human antibodies within the vascular and extracellular spaces. The volume of distribution (V_z) was 4.26 litres after a single 5 mg/kg intravenous infusion of crizanlizumab in healthy volunteers.

Biotransformation

Antibodies are primarily eliminated via proteolysis by lysosomal enzymes in the liver to small peptides and amino acids.

Elimination

In healthy volunteers, the mean terminal elimination half-life ($T_{½}$) was 10.6 days and the mean clearance was 11.7 ml/h at crizanlizumab dose level 5 mg/kg. In patients with sickle cell disease, the mean elimination $T_{½}$ during the dosing interval was 11.2 days.

Linearity/non-linearity

The exposure to crizanlizumab (mean C_{max}, AUC_{last}, or AUC_{inf}) increased in non-linear manner over the dose range of 0.2 to 8 mg/kg in healthy volunteers.

Special populations

Renal impairment

In a population PK analysis in patients with eGFR ranging from 35 to 202 ml/min/1.73 m^2, no clinically important differences in the pharmacokinetics of crizanlizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

Hepatic impairment
The safety and efficacy of crizanlizumab in patients with hepatic impairment have not been established. Crizanlizumab is a monoclonal antibody and is cleared via catabolism (i.e. breakdown into peptides and amino acids), and a change in dose is not expected to be required for patients with hepatic impairment.

Paediatric population
Pharmacokinetics in paediatric patients below the age of 16 years have not been investigated.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, tissue cross-reactivity and repeated dose toxicity.

In the 26-week repeated dose toxicity study, administration of crizanlizumab in cynomolgus monkeys at dose levels up to 50 mg/kg/dose once every 4 weeks (at least 13.5 times the human clinical exposure based on AUC in patients with sickle cell disease at 5 mg/kg once every four weeks) was generally well tolerated. There were no primary crizanlizumab-related findings on any endpoint evaluated. At 50 mg/kg, minimal to moderate inflammation of the vessels in multiple tissues considered to be an antigen-antibody complex reaction (primate anti-human antibody) was observed in 2 of 10 animals. There was one death attributed to aspiration of gastric contents following a peri-infusional reaction mediated by anti-drug-antibody-dependent hypersensitivity.

Pharmacological effects of crizanlizumab on haemodynamic and electrocardiographic parameters in the cynomolgus monkey were evaluated in the 26-week repeated dose toxicology study. Respiratory rate and neurological parameters were also assessed. There were no crizanlizumab-related effects on arterial blood pressure or on heart rate, PR, RR, QRS, QT, and heart rate corrected QT (QTc) intervals on the electrocardiograms (ECG). No rhythm abnormalities or qualitative changes were observed during the qualitative ECG assessment. There were no crizanlizumab-related effects on respiration rate or any neurological parameter evaluated.

Formal carcinogenicity, genotoxicity and juvenile toxicity studies have not been conducted with crizanlizumab.

In a 26-week repeated dose toxicity study, cynomolgus monkeys were administered crizanlizumab once every 4 weeks at doses up to 50 mg/kg (at least 13.5 times the human clinical exposure based on AUC in patients with sickle cell disease at 5 mg/kg once every four weeks). There were no adverse effects of crizanlizumab on male and female reproductive organs.

In an enhanced pre- and postnatal development study in cynomolgus monkeys, pregnant animals received intravenous crizanlizumab once every two weeks during the period of organogenesis, at doses of 10 and 50 mg/kg (approximately 2.8 and 16 times the human clinical exposure based on AUC in patients with sickle cell disease at 5 mg/kg/dose once every four weeks, respectively). No maternal toxicity was observed. There was an increase in foetal loss (abortions or stillbirths) at both doses and this was higher in the third trimester. The cause of the foetal losses in monkeys is unknown but may be due to the development of anti-drug antibodies against crizanlizumab. There were no effects on infant growth and development during the 6 months postpartum that were attributable to crizanlizumab.

Measurable crizanlizumab serum concentrations were observed in the infant monkeys at postnatal day 28, confirming that crizanlizumab, like other IgG antibodies, crosses the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate (E331)
Citric acid (E330)
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

Diluted solution

Chemical and physical in-use stability, from the start of preparation of the diluted solution for infusion until end of infusion, has been demonstrated for up to 8 hours at room temperature (up to 25°C) and at 2°C to 8°C for up to 24 hours overall.

From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, including 4.5 hours at room temperature (up to 25°C) from the start of preparation to completion of the infusion, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

10 ml concentrate for solution for infusion in a type I glass vial with a coated chlorobutyl rubber stopper sealed with an aluminium cap with a plastic flip-off disk containing 100 mg crizanlizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Adakveo vials are for single use only.

Preparing the infusion

The diluted solution for infusion should be prepared by a healthcare professional using aseptic techniques.

The total dose and required volume of Adakveo depend on the patient's body weight; 5 mg of crizanlizumab is administered per kg body weight.

The volume to be used for the preparation of the infusion is calculated according to the following equation:

$$\text{Volume (ml)} = \frac{\text{Patient's body weight (kg) x prescribed dose [5 mg/kg]}}{\text{Concentration of Adakveo [10 mg/ml]}}$$

1. Obtain the number of vials required to deliver the prescribed dose and bring them to room temperature (for a maximum of 4 hours). One vial is needed for every 10 ml of Adakveo (see below table).

Body weight (kg)	Dose (mg)	Volume (ml)	Vials (n)
40	200	20	2
60	300	30	3
80	400	40	4
100	500	50	5
120	600	60	6

2. Visually inspect the vials.
   - The solution in the vials should be clear to opalescent. Do not use if particles are present in the solution.
   - The solution should be colourless or may have a slight brownish-yellow tint.

3. Withdraw a volume equal to the required volume of Adakveo from a 100 ml infusion bag containing either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 5% and discard.
   - No incompatibilities between the diluted Adakveo solution and infusion bags composed of polyvinylchloride (PVC), polyethylene (PE) and polypropylene (PP) have been observed.

4. Withdraw the necessary volume of Adakveo from the vials and inject slowly into the previously prepared infusion bag.
   - The solution must not be mixed or co-administered with other medicinal products through the same intravenous line.

   Keep the volume of Adakveo added to the infusion bag in the range of 10 ml to 96 ml to obtain a final concentration in the infusion bag within 1 mg/ml to 9.6 mg/ml.

5. Mix the diluted solution by gently inverting the infusion bag. DO NOT SHAKE.

Administration

Adakveo diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter by intravenous infusion over a period of 30 minutes. No incompatibilities have been observed between Adakveo and infusion sets composed of PVC, PE-lined PVC, polyurethane, and in-line filter membranes composed of polyethersulfone (PES), polyamide (PA) or polysulphone (PSU).

After administration of Adakveo, flush the line with at least 25 ml sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 5%.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1476/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 October 2020
Date of latest renewal: 12 August 2022

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.