Summary of the risk management plan: Adakveo (crizanlizumab)

This is a summary of the risk management plan (RMP) for Adakveo. The RMP details important risks of Adakveo, how these risks can be minimized, and how more information will be obtained about Adakveo's risks and uncertainties (missing information).

Adakveo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Adakveo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Adakveo's RMP.

I. The medicine and what it is used for

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

It contains crizanlizumab as the active substance and is supplied as a concentrate for solution for infusion.

Further information about the evaluation of Adakveo's benefits can be found in Adakveo's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/adakveo.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Adakveo, together with measures to minimize such risks and the proposed studies for learning more about Adakveo's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

If important information that may affect the safe use of Adakveo is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Adakveo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Adakveo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table-1 List of important risks and missing information

Important identified risks	Infusion-related reactions
Important potential risks	Effects on hemostasis (hemorrhage) Immunogenicity related clinical consequences Infections
Missing information	Long-term safety Use in pregnant and breast feeding women

II.B: Summary of important risks

Table-2 Important identified risk: Infusion-related reactions

Evidence for linking the risk to the medicine	Monoclonal antibodies may cause infusion-related reactions like other infusional agents. Infusion related reactions (IRRs) are either allergic reactions to foreign proteins [generally immunoglobulin E (IgE)-mediated allergic responses] or non-immune mediated reactions. Considering the principal possibility of IRRs occurring after treatment with monoclonal antibodies and the fact that some albeit rare events were considered as IRR, this risk is considered as identified. Furthermore, based on the potential far reaching consequences due to this risk, it has been classified as important.
Risk factors and risk groups	No risk factors were identified in the patients treated with crizanlizumab who developed IRRs.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 and Section 4.8 **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:**

	Study CSEG101A2301 (STAND): A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises. Study CSEG101A2202: A phase II, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/ Hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis.

Table-3 Important potential risk: Effects on hemostasis (hemorrhage)

Evidence for linking the risk to the medicine	Published data have shown a prolonged bleeding time in mice with a genetic deficiency of P-selectin. P-selectin becomes overexpressed on the surface of stimulated platelets and is involved in platelet activation and aggregation. Non-clinical investigation of the potential effect of crizanlizumab on platelet aggregation did not reveal any bleeding events nor relevant findings in clinical pathology. Based on the mode of action, this risk is considered as a potential risk; based on the potential clinical consequences it is included as an important risk into the RMP.
Risk factors and risk groups	No risk factors were identified in the patients treated with crizanlizumab for events related to hemostasis.
Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Study CSEG101A2301 (STAND): A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises. Study CSEG101A2202: A phase II, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/ Hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis.

Table-4 Important potential risk: Immunogenicity related clinical consequences

Evidence for linking the risk to the medicine	The development of anti-drug antibodies (ADAs) is a typical consequence of the treatment with therapeutic proteins. The consequences of an immune reaction to a therapeutic protein range from transient appearance of ADAs without any clinical significance to those resulting in severe life-threatening conditions. Considering the overall low number of patients treated with crizanlizumab in the clinical trials and the potentially serious clinical consequences of ADAs on safety or efficacy, 'Immunogenicity related clinical consequences' is included as an important potential risk in the RMP and will be further evaluated.
Risk factors and risk groups	So far, no risk factors have been identified that make patients more prone to develop antibodies against crizanlizumab nor were patient groups identified that have a higher risk to develop anti-drug antibodies.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.8 **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Study CSEG101A2301 (STAND): A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises. Study CSEG101A2202: A phase II, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/ Hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis.

Table-5 Important potential risk: Infections

Evidence for linking the risk to the medicine	P-selectin, expressed on surfaces of activated endothelial cells and platelets, is an adhesion receptor for leukocytes. The role of P-selectin has been shown in studies in mice which were deficient for P-selectin due to gene-knock out. These animals exhibit a number of defects in leukocyte behavior, including elevated numbers of circulating neutrophils, virtually total absence of leukocyte rolling in mesenteric venules, and delayed recruitment of neutrophils to the peritoneal cavity upon experimentally induced inflammation. This clearly demonstrates a role for P-selectin in leukocyte interactions with the vessel wall and in the early steps of leukocyte recruitment at sites of inflammation.

	So far, no increase of the frequency of infections has been seen in clinical studies. Nevertheless due to limited clinical experience with crizanlizumab and the mode of action, infections have been included into the RMP as an important potential risk.
Risk factors and risk groups	So far, no increase of the frequency of infections has been seen. Therefore, no risk groups or risk factors have been identified
Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Study CSEG101A2301 (STAND): A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises. Study CSEG101A2202: A phase II, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/ Hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis.

Table-6 Important missing information: Use in pregnant and breast feeding women

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 **Additional risk minimization measures** None
Additional pharmacovigilance activities	**PASS Study CSEG101A2404**: Pregnancy outcomes Intensive Monitoring (PRIM): Crizanlizumab enhanced Intensive Monitoring **Study CSEG101A2405 - SCD PASS registry study:** A registry-based PASS would be performed to evaluate long-term safety, maternal complications and pregnancy outcomes by using SCD registries in the EU. The infant outcomes will be described whenever possible within these registries.

Table-7 Important missing information: Long-term safety

Risk minimization measures	**Routine risk minimization measures** None **Additional risk minimization measures** None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Study CSEG101A2301 (STAND): A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises. Study CSEG101A2202: A phase II, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/ Hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis. **Study CSEG101A2405: SCD PASS registry study:** A registry-based PASS would be performed to evaluate long-term safety, maternal complications and pregnancy outcomes by using SCD registries in the EU. The infant outcomes will be described whenever possible within these registries.

II.C: Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

Table-8 Studies which are conditions of the marketing authorization

Study short name	Rationale and study objectives
Study CSEG101A2301 (STAND): (Post Authorisation Efficacy Study)	This study is designed to confirm efficacy and safety of crizanlizumab 5 mg/kg dose and assess safety and efficacy of a higher dose (7.5 mg/kg).
Study CSEG101A2202 (Post authorization safety study)	The purpose of this study is to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of crizanlizumab and to evaluate the safety of crizanlizumab in sickle cell disease patients.

II.C.2. Other studies in post-authorization development plan

Table-9 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CSEG101A2301 (STAND): **(Post Authorisation Safety Study)**	This study is designed to confirm efficacy and safety of crizanlizumab 5 mg/kg dose and assess safety and efficacy of a higher dose (7.5 mg/kg).

CSEG101A2404: Crizanlizumab Pregnancy outcomes Intensive Monitoring (PRIM) (enhanced pharmacovigilance program) (Post Authorisation Safety Study)	The overall objective of the crizanlizumab PRIM program is to collect data on pregnancy outcomes in patients treated with crizanlizumab during pregnancy or within 105 days before the last menstrual period (LMP). Data on infant outcomes at 3 and 12 months post-delivery will also be collected.
CSEG101A2405: SCD PASS registry study:	A registry-based PASS would be performed to evaluate long-term safety, maternal complications and pregnancy outcomes by using SCD registries in the EU. The infant outcomes will be described whenever possible within these registries.