ADAKVEO®▼ (crizanlizumab): revocation of EU marketing authorisation due to lack of therapeutic efficacy

Dear Healthcare Professional,

Novartis, in agreement with the European Medicines Agency (EMA) and <National Competent Authority>, would like to inform you of the following:

Summary

- **The phase III study (STAND) of Adakveo in sickle cell disease patients with vaso-occlusive crises did not confirm its clinical benefit.**
- **As a consequence, the benefit-risk balance of Adakveo is no longer favourable and the marketing authorisation in the EU will be revoked.**
- **No new patients should be started on Adakveo in the EU. Prescribers should inform patients currently on treatment with Adakveo, and discuss alternative treatment options with them.**

Background Information

Adakveo was authorised in the European Union in October 2020 for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease (SCD) patients aged 16 years and older. It could 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. At time of its approval in the EU, data supporting the effects of Adakveo were not considered comprehensive due to some uncertainty about the size of Adakveo's effect. The medicine was therefore granted a marketing authorisation on condition that the company provided data from the STAND (CSEG101A2301) study[1] in order to confirm the efficacy and safety of the medicine.

EMA's human medicines committee (CHMP[2]) assessed the results of the STAND study and concluded that the study did not confirm the clinical benefit of Adakveo. Specifically, the study did not show a difference between Adakveo (2.49, 95% CI [1.90, 3.26]) and placebo (2.30, 95% CI [1.75, 3.01]) in annualized rates of VOCs leading to a healthcare visit over the first-year post randomisation. Rate ratio was 1.08, 95% CI (0.76, 1.55) in crizanlizumab 5.0 mg/kg versus placebo. There was no clinical benefit in key secondary efficacy endpoint (adjusted annualised rates of VOCs leading to healthcare visit and treated at home combined): the rates were 4.70, 95% CI: (3.60, 6.14) in crizanlizumab 5.0 mg/kg arm versus 3.87, 95% CI: (3.00, 5.01) in the placebo arm; rate ratio was 1.21, 95% CI (0.87, 1.70) in crizanlizumab 5.0 mg/kg versus placebo.

[1] STAND Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (NCT03814746)
[2] Committee for Medicinal Products for Human Use

No new safety concerns were identified. However, there were higher rates of grade ≥3 treatment related adverse events as well as of serious related adverse events for crizanlizumab compared to placebo.

In addition to the STAND study, data from other studies, a managed access program and real world data were reviewed. However, the studies had several limitations, such as their design as single-arm studies, and therefore did not allow to conclude on an effect of Adakveo and were not sufficient to overcome the negative results of the STAND study.

In conclusion, as the STAND study did not confirm its clinical benefit, the CHMP concluded that the benefit-risk balance of Adakveo is no longer favourable and the conditional marketing authorisation will be revoked in the EU.

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system><For biological medicinal products, also include a reminder to report the product name and batch details>. <Mention if product is subject to additional monitoring and the reason why>

Company Contact Point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Adakveo (crizanlizumab)
Marketing authorisation holder(s)	Novartis Europharm Ltd.
Safety concern and purpose of the communication	Inform healthcare professionals of the revocation of the conditional marketing authorization of crizanlizumab in EU due to lack of therapeutic efficacy.
DHPC recipients	Haematologists, prescribers and hospital pharmacists and nurses. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU/EEA countries.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP	25 May 2023
Submission of translated DHPCs to the national competent authorities for review	05 June 2023
Agreement of translations by national competent authorities	09 June 2023
Dissemination of DHPC	15 June 2023