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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

15th June 2023

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 the Health Products Regulatory Authority (HPRA), 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

[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

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.

No new safety concerns were identified. However, there were higher rates of grade ≥3 treatment related adverse events as well as 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

This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product.

All suspected adverse reactions should be reported to HPRA Pharmacovigilance at www.hpra.ie

Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling 01 2080612.

Company Contact Point

If you require any further information, please contact:

Medical Information at medinfo.dublin@novartis.com
Drug Safety Hotline 01 2080612

Yours Sincerely

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