10-Jan-2024

Direct Healthcare Professional Communication (DHPC)

ADAKVEO ▼ (crizanlizumab): revocation of UK marketing authorisation due to lack of therapeutic efficacy as determined by MHRA

Dear Healthcare Professional,

Novartis, in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA), 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 considered favourable by the MHRA and the conditional marketing authorisation in the UK will be revoked.**
- **No new patients should be started on Adakveo in the UK. Prescribers should inform patients currently on treatment with Adakveo and discuss alternative treatment options with them.**

Background Information

Adakveo received conditional approval in October 2020 for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease (SCD) patients aged 16 years and older 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, 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), Phase III study[1] in order to confirm the efficacy and safety of the medicine.

The MHRA 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

[1] STAND Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (NCT03814746)

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 of serious related adverse events for crizanlizumab compared to placebo.

In addition to the STAND study, data from other studies, including real-world data from a Global Managed Access Program (Crizanlizumab Cohort MAP) were reviewed by MHRA. Given that these studies were single arm, MHRA did not deem the data generated in these studies comprehensive.

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

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

You can report via:

- the Yellow Card website
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, timing onset, treatment dates, investigation results, and product brand name.

The non-identical nature of biological medicines and vaccines means it is very important that safety surveillance is carried out on a brand/product-specific basis. When reporting a suspected ADR to a biological medicine (such as blood products, antibodies and advanced therapies [such as gene and tissue therapy]) or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch-number.

Additionally, when providing patients with details of the vaccine or biological medicine administered, it is good practice to give them details of the brand and batch number. This will allow patients and carers to more accurately report suspected ADRs to the Yellow Card scheme.

Company contact point

If you have any questions or require further information, please contact the Novartis Medical Information department on 01276 698370 or email medinfo.uk@novartis.com.

Adverse events should also be reported to Novartis via the online pharmacovigilance intake (PVI) tool at www.report.novartis.com or uk.patientsafety@novartis.com.

- Adakveo (Crizanlizumab)▼ is subject to additional monitoring. This will allow quick identification of new safety information
- Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme

Yours faithfully,

Annae Liu
Haematology Medical Director
Novartis Pharmaceuticals UK Ltd

In accordance with our Privacy Notices (novartis.com/uk-en/privacy-policy). Novartis is providing you with this letter to provide you with updated information about the results from the Phase III study CSEG101A2301 (STAND).