NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Committee for Human Medicinal Products (CHMP) made by the European Commission (EC):

Product(s) Name(s)	Adakveo
Active substance(s)	crizanlizumab
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Novartis Europharm Limited

Background

Adakveo contains crizanlizumab, a selective IgG2 kappa humanised monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks the interaction with its ligands. In the chronic pro-inflammatory state associated with sickle cell disease, P-selectin is over-expressed. P-selectin-mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and vaso-occlusive crises (VOC).

It is a centrally authorised product 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.

Adakveo 10 mg/ml was granted a conditional marketing authorisation (CMA) on 28 October 2020, based on primary analysis results of median annual rate of VOC leading to a healthcare visit of the pivotal phase 2 study (Study A2201, SUSTAIN). This was a phase II multicentre, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of crizanlizumab with or without HU therapy in sickle cell disease patients with sickle cell-related pain crises.

At the time of granting the CMA, efficacy data was available from the SUSTAIN study. In this study, the primary endpoint for the 5 mg/kg dose (the only dose approved) was met, with a 45.3% lower median annual rate of VOC leading to a healthcare visit compared to placebo considering the ratio of the standard median of 1.63 VOCs in 5 mg/kg crizanlizumab group (N=67) compared to 2.98 VOCs in placebo (N=65). The point estimate of the two-sample Hodges-Lehmann (HL) median annual rate of sickle cell pain crises (SCPC) estimator was -1.01 (95% confidence interval (CI) [-2.00, 0.00], p=0.010).

Overall, a positive benefit-risk balance was considered established based on the totality of evidence and subject to additional confirmatory efficacy and safety data to be generated in the context of a CMA.

In order to generate comprehensive data with SEG101, the marketing authorisation holder (MAH) was requested to submit by December 2025 the results of the primary analysis of a phase III A2301 study (STAND) of crizanlizumab with or without HU/HC in adolescent and adult sickle cell disease patients with vaso-occlusive crises (specific obligation). In addition to confirming the efficacy and safety data of crizanlizumab in the 5 mg/kg dose, this study was planned to assess whether a higher dose (7.5 mg/kg) of crizanlizumab could further reduce the frequency of VOCs.

Issues to be considered

In December 2022, the first interpretable results of the STAND study were communicated by the MAH. These results show that neither the primary nor the key secondary endpoint (i.e. annualized rates of VOC leading to healthcare visit, or leading to healthcare visit and treated at home combined) with crizanlizumab were met. The adjusted annualized rates of VOC leading to healthcare visit over the first-year post randomization estimated via negative binomial regression were 2.49, 95% CI: (1.90, 3.26) in crizanlizumab 5.0 mg/kg arm, versus 2.30, 95% CI: (1.75, 3.01) in the placebo arm. The median annualized rates of VOC leading to healthcare visit were 2.0 in crizanlizumab 5.0 mg/kg arm, and 1.0 in the placebo arm. No statistically significant differences between crizanlizumab arms and placebo arm in the annualized VOC rates leading to healthcare visit over the first year post randomization were observed for the primary and key secondary endpoints. The preliminary results do not suggest new safety concerns with crizanlizumab. However, higher rates for grade ≥3 treatment related adverse events were reported for crizanlizumab compared to placebo.

At this stage, the definitive causative factor(s) to explain the observed results cannot be identified. However, these preliminary results showing a potential lack of efficacy raise uncertainty as to whether the benefit of crizanlizumab still outweighs its risks in its authorised indication.

In light of the current emerging data, there is a need to review the findings in the context of all available data and assess their potential impact on the benefit-risk of Adakveo in its approved indication.

In view of the above, the EC initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product Adakveo (crizanlizumab). The EC requests the Agency/CHMP to give its opinion by 31 July 2023 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

In addition, the EC requests the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product.

Signed Date
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General