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 CHMP made by the European Commission (EC):

Product(s) Name(s)	Tecovirimat SIGA
Active substance(s)	tecovirimat
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	SIGA Technologies Netherlands B.V.

Background

Tecovirimat inhibits the activity of the orthopoxvirus VP37 protein, which is encoded by a highly conserved gene in all members of the orthopoxvirus genus. Tecovirimat blocks the interaction of VP37 with cellular Rab9 GTPase and TIP47, which prevents the formation of egress competent enveloped virions necessary for cell-to-cell and long-range dissemination of virus.

On 6 January 2022, Tecovirimat SIGA was granted a marketing authorisation under exceptional circumstances pursuant to Article 14(8) of Regulation (EC) No. 726/2004. It is indicated for the treatment of smallpox, monkeypox and cowpox, in adults and children with body weight at least 13 kg. It is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg. It should be initiated as soon as possible after diagnosis, in accordance with official recommendations.

The benefits of Tecovirimat SIGA in humans were predicted from studies in animal models of orthopoxvirus disease. At the time of the initial assessment, no clinical studies were conducted due to the nature of the viruses to be treated and their lack of or rare circulation in humans. Human pharmacokinetic (PK) and PK-pharmacodynamic supported the clinical posology.

In that regard, specific obligations to complete two post-authorisation measures were imposed. One of these measures consists in the provision of yearly updates on any new information concerning the safety and efficacy of tecovirimat in the treatment of the smallpox, mpox, cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox, in adults and children with body weight at least 13 kg.

Issues to be considered

In the ongoing third annual re-assessment (EMA/S/0000248804), new efficacy data have emerged.

In particular, high-level results of the completed PALM007[1] and STOMP[2] randomized, placebo-controlled, double-blind trials of tecovirimat for the treatment of human monkeypox virus[3] disease, both sponsored by the United States National Institutes of Health's National Institute of Allergy and Infectious Diseases, have been published in August 2024 and December 2024 respectively. The results of PALM007 were further published in the New England Journal of Medicine in April 2025[4]. A preliminary review of the available data suggests that the studies did not meet the primary endpoint, as tecovirimat did not significantly reduce the number of days to lesion resolution in patients with mpox compared to placebo. It also appears that in both trials there was no treatment benefit with respect to the secondary endpoint (e.g. depending on the trial: pain reduction, time to lesion healing and mortality).

In these studies, tecovirimat was well-tolerated with no drug-related serious adverse events.

Additional analyses are planned to better assess outcomes observed in the studies. These include whether there were any significant differences in clinical outcomes by days of symptoms prior to enrolment, severity of clinical disease, participant characteristics (people with compromised immune systems, children, and people who are pregnant are especially vulnerable to severe mpox regardless of the virus clade), or the genetic variant of mpox being treated.

While full datasets are not yet available, this new information raises concern regarding a possible lack of efficacy of Tecovirimat SIGA in the mpox indication. Furthermore, considering that the majority of studies underlying the granting of the marketing authorisation in all the authorised indications for Tecovirimat were conducted in cynomolgus monkeys, similar concerns regarding the other authorised indications cannot be ruled out.

On 21 July 2025, high level results of the UNITY trial evaluating tecovirimat with a similar study design to STOMP were published[5] and appear to be consistent with those from STOMP and PALM007. It is noted that there are other mpox clinical trials with tecovirimat ongoing or recently completed (e.g. PLATINUM Canada and UK, EPOXI(EU)). Results are not yet available from these studies.

The findings from these emerging and forthcoming data need to be reviewed, taking into account all available data, to determine whether there is an impact on the benefit-risk balance of Tecovirimat SIGA in the authorised indications.

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 Tecovirimat SIGA authorised under exceptional circumstances. The EC requests the Agency/CHMP to give its opinion by 31 May 2026 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

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1 https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo

2 https://www.nih.gov/news-events/news-releases/nih-study-finds-tecovirimat-was-safe-did-not-improve-mpox-resolution-or-pain

3 Clade I (PALM007) and clade II (5TOMP). Clade II caused a global mpox outbreak in 2022, and clade I outbreak in 2024 in Central and East African countries was declared a public health emergency of international concern by the World Health Organization

4 PALM007 Writing Group. Tecovirimat for Clade I MPXV Infection in the Democratic Republic of Congo. N Engl J Med. 2025 Apr 17;392(15):1484-1496.

5 https://mpx-response.eu/large-international-trial-unity-reports-no-clinical-benefit-from-tecovirimat-for-mpox-resolution/

In addition, the EC requests the Agency 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

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Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General