Annex IV

Scientific conclusions

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In the context of the third annual re-assessment of the marketing authorisation under exceptional circumstances for Tecovirimat SIGA (EMA/S/0000248804), a preliminary review of the available data from the completed PALM007[1] and the STOMP[2] trials of tecovirimat for the treatment of mpox (previously referred to as monkeypox, while the virus that causes mpox continue to be referred to as monkeypox virus (MPXV) suggested that the studies did not meet their primary or secondary endpoints. While full datasets were not yet available, this new information raised concerns regarding a possible lack of efficacy of Tecovirimat SIGA in the mpox indication. Furthermore, similar concerns regarding the other authorised indications could not 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[3] and appeared to be consistent with those from STOMP and PALM007. Other mpox clinical trials with tecovirimat were ongoing or recently completed, but results were not yet available from these studies.

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

On 23 July 2025 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Tecovirimat SIGA and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

At the time of marketing authorisation, it was not possible to provide comprehensive data on the efficacy and safety of tecovirimat under normal conditions of use, because the indications in which it became authorised were encountered too rarely, and it would have been contrary to generally accepted principles of medical ethics to collect such information. The authorisation was therefore predominantly based on non-clinical (animal) studies, supported by human pharmacokinetic (PK) and safety studies. The benefits of Tecovirimat SIGA in humans were predicted from studies in animal models of orthopoxvirus diseases. These studies, combined with the mechanism of action of tecovirimat, in vitro pharmacology evaluations demonstrating antiviral activity against a number of orthopoxviruses, and the highly conserved drug target, provided the basis for including the four indications. The non-clinical studies demonstrated significant survival benefit, reduced lesion burden and lowered viremia with tecovirimat treatment. The lethal non-human primate (NHP) models, originally developed to mimic smallpox in humans and powered for mortality, demonstrated efficacy even once lesions had developed. However, these data indicated that tecovirimat should be used as soon as possible after diagnosis, in accordance with official recommendations.

In order to ensure adequate monitoring of safety and efficacy of tecovirimat in its authorised indications, the marketing authorisation holder (MAH) was required as a specific obligation to provide yearly updates on any new related information. In the present review, the CHMP considered all available data, including from randomised controlled trials (RCT) (PALM007, STOMP, UNITY, PLATINUM UK), access programmes (CAR and CDC) and an observational study (MOSAIC), PK data, preclinical efficacy data (in vitro and in vivo, including new interim results of a Clade II intravenous MPXV challenge in NHPs) and the literature. Complete data was available from PALM007, and reasonably

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

complete data from STOMP. Therefore, while the complete data was not available from all trials, in view of the results available, it is considered unlikely that the future and final data of the RCT trials would alter the assessment conclusions. The CHMP also considered the views expressed by the Scientific Advisory Group (SAG) on Vaccines and Therapies for Infectious Diseases.

All RCTs were of a similar general double blind, placebo-controlled trial design based on the world health organization (WHO) core protocol. No outcome data was available to date from the open label arms of the trials that included higher risk patients. PALM007 recruited a similar number of hospitalised male and female patients with a median age of 11 years, with clade I mpox. The three other trials recruited predominantly adult male patients with clade II mpox, overall reflecting the 2022 outbreak patterns of mainly sexual transmission between men who have sex with men. Most of the patients were advanced in their illness at the time of starting trial treatment (median time from symptom onset to treatment initiation was 6 days in PALM007, 8 days in STOMP, 9 days in UNITY and 7 days in PLATINUM-UK).

Overall, there were no significant differences between the tecovirimat and placebo arms across the RCTs for lesion resolution and other endpoints such as mortality, virological outcomes and pain/use of analgesia. There were positive trends favouring tecovirimat treatment over placebo observed across some of the RCTs, such as earlier lesion resolution in patients with more than 100 lesions at baseline or when treatment was started within 4 days of symptom onset in PALM007. However, these results were derived from post-hoc sensitivity analyses and were not statistically significant. It is also important to recognise the methodological limitations of the RCTs, such as limited control over identification of symptom onset and determination of clinical resolution.

Immunocompromised patients are considered most at risk of a severe or protracted viral course, and therefore most likely to require antiviral treatment. However, there are data from animal studies that suggest that tecovirimat may have reduced efficacy in immunocompromised patients, while data from the open label arms of the studies are not yet available. Furthermore, resistance mutations have arisen in patients receiving prolonged tecovirimat treatment for mpox, particularly in immunocompromised patients. While current data suggest the absolute risk remains low, the potential for avoidable selective pressure warrants acknowledgement in the context of repeated or unnecessary prescribing. Whilst these findings relate to mpox, they are considered of potential relevance generally for tecovirimat use in the treatment of orthopoxvirus infections, and the product information is updated accordingly.

Across the four RCTs the incidence of treatment-emergent adverse events was broadly similar between tecovirimat and placebo groups. Serious adverse events were infrequent and generally balanced between treatment arms. Despite limitations in the collection of some of this safety data (e.g. relatedness was not assessed or reported, safety data not provided by demographic subgroups), the data available provide a broadly reassuring safety profile for tecovirimat in the treatment of mpox across diverse clinical settings, with no new safety signals identified. The safety of tecovirimat in subgroups with demographics/clinical characteristics that are associated with a more severe disease course is less well characterised.

Benefit-risk balance in mpox

Considering that tecovirimat is expected to block the dissemination of the virus, the MAH argues that in order to see an effect, treatment should be initiated on or before peak viremia. By inclusion criteria, most patients in the trials had active lesions suggesting peak-viral load had passed. Tecovirimat was administered on average 6-9 days after reported symptom onset.

In support of this hypothesis, the MAH performed post-hoc longitudinal analyses of lesion count in PALM007, which demonstrated nominally statistically significant lower lesion counts for the tecovirimat arm compared to the placebo arm, in particular for patients treated ≤4 days and 5 days from symptom

onset and patients with baseline lesion counts ≥100. The MAH proposed to specify in section 4.2 of the summary of product characteristics (SmPC) that for the treatment of mpox, tecovirimat should be administered as early as possible, and no later than 5 days after symptom onset. However, while these results suggest positive effects, they are exploratory, and these subgroups were not prespecified. Further, these findings have not been corroborated in the other trials. In most trials there were too few patients dosed early after symptom onset to conclude on any potential trends towards a better outcome with earlier treatment. In addition, some uncertainty is noted across the trials regarding the definition of symptom onset, and the accuracy of self-reported lesion assessment, which weakens the subgroup analyses.

The results of the new nonlethal NHP study 25-06 conducted in a new model using clade II MPXV characterised by low mortality (<1%) and lesional disease, better reflecting the human mpox phenotype, showed that tecovirimat's antiviral effects were strongly dependent on the timing of administration. Most benefits were achieved when treatment was initiated prior to the appearance of lesions. The most pronounced antiviral activity, as measured by suppression of progressive lesions, maximal total lesion formation, and viral loads occurred when treatment was initiated on day 2, before lesions appeared. Study SR10-0037F that supported the initial marketing authorisation had shown a drop off in efficacy when treatment was started in NHPs on the sixth day post intravenous MPXV challenge. Therefore, CHMP agreed that the non-clinical data indicate that the timing of tecovirimat treatment may be critical. However, in the non-clinical studies, treatment was administered at given time points post intravenous challenge, rather than post symptom onset. Whereas, as also noted by the SAG, dating the infection in humans is complicated. Furthermore, there are no data on the temporal correlation between intravenous exposure and infection at the mucosal surface. Therefore, while informative, these data are insufficient to define a therapeutic window for tecovirimat administration in the treatment of mpox, considering the clinical results available.

Further, the CHMP and the SAG agreed that peak viraemia in mpox tends to occur early and has generally passed by the time of lesions onset. However, as mpox viral replication is mostly located in the mucosal surface (at least for clade IIb), viraemia is not the most reliable marker for mpox lesion onset or progression, as flagged by the SAG and agreed by CHMP.

Therefore, whilst the CHMP considered plausible that the reason for tecovirimat not showing efficacy in the treatment of mpox in the RCTs may have been the design and treatment conditions (specifically the timing of starting tecovirimat), the evidence currently available is insufficient to establish the efficacy of tecovirimat given at an earlier timepoint, or to identify what might be the correct therapeutic window (provided that there is one). The SAG was also of the view that an appropriate treatment window for treatment of mpox with tecovirimat cannot be defined based on the currently available clinical data.

The CHMP and the SAG also noted that while increased public awareness (e.g. through engagement of the community) could quicken treatment initiation, starting treatment within 5 days of symptom onset was mostly not feasible in the clinical trials, and would remain challenging in clinical practice as there is currently no standard point of care testing for rapid diagnosis.

The CHMP concluded that the benefit-risk balance of Tecovirimat SIGA was no longer favourable in the mpox indication.

Benefit-risk balance in the other indications

The viral dynamics and disease courses of smallpox, cowpox, and vaccina virus are each different to mpox, despite their structural similarities. Therefore, the efficacy results from the mpox RCTs are not considered of direct relevance for the demonstration of efficacy of tecovirimat in the three other authorised indications. Overall, in the absence of negative clinical efficacy data, as is now available for

mpox, the in vitro and animal data that supported the initial marketing authorisation in the smallpox, cowpox and vaccina virus indications are still considered relevant and should be predictive of the efficacy of tecovirimat in treating these viruses in humans. It is noted that currently, clinical studies continue not to be possible in these indications due to eradication (smallpox), or very low incidences (cowpox, vaccinia). Further the early timing of treatment in the animal studies reflects a realistic human scenario for smallpox where rapid diagnosis and treatment are prioritised.

The CHMP concluded that the benefit-risk balance of Tecovirimat SIGA remains favourable in these indications, subject to annual reassessment and satisfactory adherence to the specific obligations in place. Early onset of treatment for all viruses is considered important and the current general advice in the SmPC section 4.2 to start treatment as soon as possible is considered adequate in the absence of clinical data with these viruses, given that the viral kinetics and clinical course of these viruses are not the same as those of human mpox virus.

The CHMP considered that minor clarifications were needed in section 4.2 and 5.1 of the SmPC, and typographic errors were corrected.

Conclusion

Overall, the CHMP considers that the benefit-risk balance of Tecovirimat SIGA in the treatment of mpox is no longer favourable. No new significant information has become available regarding the benefit-risk balance of Tecovirimat SIGA for the treatment of adults and children with body weight at least 13 kg with smallpox, cowpox, and complications due to replication of vaccinia virus following vaccination against smallpox. Therefore, the committee recommends the variation to the terms of the marketing authorisation.

CHMP opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Tecovirimat SIGA (tecovirimat).
- The CHMP reviewed the available data from clinical trials, taking into account all available data submitted by the MAH, as well as the views expressed by the Scientific Advisory Group on Vaccines and Therapies for Infectious Diseases.
- The CHMP noted the in vitro data and studies in animal models of orthopoxvirus diseases that predicted the benefits of Tecovirimat SIGA in humans for the initial marketing authorisation.
- Across the randomised clinical trials, CHMP noted the absence of significant differences between the tecovirimat and placebo arms for mpox lesion resolution and other endpoints such as mortality, virological outcomes and pain. The CHMP concluded that Tecovirimat SIGA lacks efficacy under the conditions studied in these mpox trials.
- The CHMP considered it plausible that this is due to the late timing of treatment administration in these trials. However, the evidence currently available is insufficient to establish the efficacy of tecovirimat in the authorised indication for the treatment of mpox in any therapeutic window.
- Therefore, the CHMP concluded that the benefit-risk balance of Tecovirimat SIGA is not favourable in the mpox indication.
- The CHMP also concluded that no new significant information has become available regarding the benefit-risk balance of tecovirimat for the treatment of adults and children with body weight at least 13 kg with smallpox, cowpox, and complications due to replication of vaccinia

virus following vaccination against smallpox. Nevertheless, information on resistance development with mpox, considered potentially relevant to the use in these indications, is updated in the product information.

In view of the above, the Committee considers that the benefit-risk balance of Tecovirimat SIGA remains favourable subject to the revision to the agreed conditions to the marketing authorisation and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Tecovirimat SIGA (tecovirimat).