EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Torisel

temsirolimus

Procedure number: EMEA/H/C/000799/A20/0051

Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

The US Food and Drug Administration informed the European Medicines Agency that following an inspection, concerns have been raised about the conduct of bio-analytical studies performed by the Cetero research facilities in Houston (Texas, USA) during the period from April 2005 to June 2010. The inspection identified significant instances of misconduct and violations of federal regulations, including falsification of documents and manipulation of samples.

In the European Union, it was identified that this could potentially impact the marketing authorisation of Torisel.

On 16 November 2011 the European Medicines Agency (EMA) informed relevant MAHs that the Food and Drug Administration had raised concerns, following its inspection of Cetero Research facilities in Houston (Texas, USA), on the conduct of bio-analytical studies in the period between April 2005 and June 2010. The EMA asked MAH of all centrally authorised medicinal products to identify the products for which the marketing authorisation dossier included studies conducted at the above mentioned facility.

The MAH for Torisel provided responses on 14 December 2011.

On 2 May 2012, the FDA informed the EMA of a letter sent to Cetero confirming that, based on the final results of the inspection, the period of concern for which data generated by Cetero was considered potentially unreliable and for which the FDA recommended actions to be taken is from April 2005 to August 2009.

A Rapporteur's assessment report on the MAH's responses was circulated on 5 July 2012.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 16 July 2012 to assess whether the deficiencies in conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) have impact on the benefit-risk balance of Torisel, and to give its opinion on whether measures are necessary to ensure the safe use of the product and specifically on whether the marketing authorisation for Torisel should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Torisel (temsirolimus) is a specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. Temsirolimus exerts its effect on cell proliferation by inhibiting mTOR-dependent protein translation induced by growth factor stimulation of cells. In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia inducible factors, HIF-1 and HIF-2 α. These transcription factors regulate the ability of tumors to adapt to hypoxic microenvironments and to produce the angiogenic factor vascular endothelial growth factor (VEGF).

Temsirolimus first received marketing authorization in the European Union (EU) on 19 November 2007 for first-line treatment of patients with advanced renal cell carcinoma who have at least 3 of 6 prognostic risk factors. Subsequently, temsirolimus was approved in the EU also for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.

Study 3066K1-155-US entitled "A Single-Dose, Single-Blind, Placebo- and Moxifloxacin-Controlled 2-Period, Randomized, Crossover, 3rd Period Sequential Study Of The Effects Of Temsirolimus On Cardiac repolarization In Healthy Subjects" was a QTc study of temsirolimus where part of the analysis were conducted by the concerned laboratory Cetero Research.

2.1. Clinical aspects

Study 3066K1-155-US

The final study report of study 3066K1-155-US was submitted as part of the marketing authorisation application.

Participants in the study received either temsirolimus or placebo or moxifloxacin as positive control.

The primary endpoint was to compare the effect on QTc interval between temsirolimus 25 mg single dose and placebo at 0.5 hours. The secondary endpoint was to characterise the PK/PD relationship.

In this study, the plasma concentrations of moxifloxacin at 2 and 24 hours were used as positive control and were analysed at Ba Research International (Houston, Texas), now part of Cetero. The analyses were performed between 19 and 21 July 2006.

The ECGs used to measure the primary endpoint parameters were electronically/digitally recorded by a third party vendor. Plasma concentrations of temsirolimus and sirolimus were also analysed by a different laboratory. Therefore any potential impact will be restricted to the plasma concentrations of the control moxifloxacin.

As noted in the study report, '*the presence of moxifloxacin did have a statistically significant positive effect by increasing the QTc interval. Notwithstanding, concentrations of moxifloxacin at the 2- and 24-hour timepoints, however, were approximately a third of the concentrations reported in the moxifloxacin product label. The reason for this lower than expected exposure, however, is unclear*.'

It can therefore be concluded that, while obvious discrepancies were noted for the control moxifloxacin between the plasma concentrations measured and the expected according to the product information, the validity of the primary endpoint determined by ECG measurements of temsirolimus was not affected by this issue.

Additional data on QTc prologation

The preclinical hERG channel data available as part of the marketing authorisation dossier does not suggest that temsirolimus had torsadogenous potential by inhibition of hERG channel fluxes.

Routine monitoring of the potential risk for QTc interval prolongation is included in the Risk Management Plan. Known frequency of reporting of QT prolongation/torsades de pointes is 0.7% and 2.3%, respectively.

A renewal procedure is ongoing in parallel and includes a request for QT prolongation/torsades de pointes to be the object of a specific analysis in upcoming PSURs.

3. Overall discussion and benefit/risk assessment

Data from the preclinical and clinical studies, and also from post-authorisation safety monitoring, are consistent and do not indicate a significant potential for QT prolongation/torsades de pointes.

Nevertheless routine monitoring of the potential risk for QTc interval prolongation is included in the Risk Management Plan and will be discussed in upcoming PSURs.

In study 3066K1-155-US, only the plasma concentrations of the positive control moxifloxacin were analysed by Cetero. As the ECG parameters and the plasma concentrations of temsirolimus and sirolimus were determined in different facilities, the results of the study continue to be valid.

The CHMP therefore concluded that the potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities have no impact on the benefit-risk of Torisel.

4. Conclusion and grounds for the recommendation

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Torisel, initiated by the European Commission.
- The Committee reviewed the relevant data from preclinical and clinical studies, and from post-authorisation safety monitoring.
- The Committee concluded, in view of available data, that any potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities do not impact on the benefit-risk balance of Torisel.

The Committee, as a consequence, concluded that the benefit-risk balance of Torisel remains positive under normal conditions of use.