European Medicines Agency

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ASSESSMENT REPORT
FOR
Torisel

International non-proprietary name/Common name:
temsirolimus

Procedure No. EMEA/H/C/000799/II/0001

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

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SCIENTIFIC DISCUSSION

Introduction

Torisel (temsirolimus) was first granted a marketing authorisation in the EU on 19 Nov 2007 for first-line treatment of patients with advanced Renal Cell Carcinoma (RCC) who have at least 3 of 6 prognostic risk factors.

This type II variation concerns an extension of the indication for Torisel to add the new therapeutic indication: *"treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL)"*.

Torisel (temsirolimus) is a selective inhibitor of mTOR (mammalian target of rapamycin), a serine/threonine kinase involved in controlling many cellular functions, such as cell proliferation, cell survival, protein synthesis and transcription. Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-temsirolimus complex inhibits the activity of mTOR that controls cell division. In treated tumour cells, inhibition of mTOR activity results in a G1 growth arrest caused by the disruption of translation of regulatory cell cycle proteins (D-type cyclins, c-myc, and ornithine decarboxylase). When mTOR is bound to the temsirolimus-FKBP-12 complex, its ability to phosphorylate and control the activity of protein translation factors that regulate cell division (4E-BP1 and S6K), is blocked. These protein translation factors are both downstream of mTOR in the P13 kinase/AKT pathway.

In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha. These transcription factors regulate the ability of tumours to adapt to hypoxic microenvironments and to produce the angiogenic factor VEGF. Even though cyclin D1 mRNA is constitutively expressed in mantle cell lymphoma (MCL), it is potentially subject to translational regulation by a pathway involving the mammalian target of rapamycin (mTOR). In mantle cell lymphoma, mTOR kinase regulates mRNA translation by phosphorylation of two critical substrates—eukaryotic initiation factor 4E binding protein and p70S6 kinase. These phosphorylation events enhance translation of cyclin-D1 mRNA into cyclin-D1 protein.

Scope of the variation

This type II variation concerns an extension of indication to add treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). Based on the results of the clinical development program for MCL, the recommended dosing regimen is different from that in advanced renal cell carcinoma. In this context, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SPC have been amended and the Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to make some minor editorial changes to the annexes and to update the contact details of the UK local representative in the Package Leaflet. The MAH has also updated annex IIB to include the version number of the latest Risk Management Plan (version 2.4) agreed with the CHMP.

This application is based on the final clinical study report for a phase 3 study in patients with relapsed and/or refractory MCL (study 3066K1-305-WW). In addition the following reports were included as part of the application:
- Population PK Analysis (CSR-70829): This is a summary of studies 3066K1-305-WW, 3066K1-124-US, -145-US, -200-US, and -203-EU;
- Study 3066K1-147-US (final clinical study report): a biomarker study in head and neck cancer that was ongoing at the time of the MAA for RCC;
- Study 3066K1-402-WW (final clinical study report): A completed phase 1/2 study of temsirolimus in combination with sunitinib;
- Study 3066K1-139-US (updated progress report): An ongoing study in paediatric patients, previously reported in the RCC MAA.

Mantle cell lymphoma

Non-Hodgkin Lymphomas can be seen as two major prognostic groups: the indolent lymphomas and the aggressive lymphomas. Mantle cell lymphoma (MCL) is a specific entity of B-cell lymphoma defined by the REAL classification (1994) and by the WHO classification (2001). The entity corresponds to the centrocytic lymphomas as defined previously by the Kiel classification (1988). Although MCL belongs to the group of indolent lymphomas the clinical course is rather more aggressive than in other entities of indolent lymphomas.

MCL accounts for approximately 8% of all lymphoma diagnoses. Patients with MCL are typically older adults with a male predominance and usually present with stage IV disease. The cells are characterized as $CD20^{+}$ $CD5^{+}$ $CD23^{-}$ with a t(11;14)(q13;q32) and cyclin D1 overexpression on immunohistochemistry. Response to chemotherapy usually results in a tumour response but unmaintained remissions are short and the median survival is 3 to 4 years. The treatment approach to newly diagnosed patients with MCL depends on the patient's eligibility for stem cell transplantation (SCT). Those who are eligible are usually treated with either rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by SCT or high dose cytarabine or other regimens such as HyperCVAD (cyclophosphamide, vincristine, doxorubicin, decadron, cytarabine, and methotrexate). The purine nucleoside analogues also have activity as single agents and with rituximab. Unfortunately none of these approaches can definitively cure patients with MCL, and new agents are needed.

In 2006, Velcade (bortezomib) was approved in the United States for use in patients with MCL who have had at least 1 prior treatment. Bortezomib was approved on the basis of data from 155 patients in 1 single-group phase 2 study because it demonstrated objective response benefits. The ORR was 33% and patients with response had a median duration of response of 9.2 months, and updated results report a median OS of 23.5 months for this single arm study.

In the EU there are no approved treatments for relapsed MCL. However, there are a number of cytotoxic medicinal agents that are approved for Non-Hodgkin Lymphoma in general or for indolent Non-Hodgkin Lymphoma, including anthracycline, alkylating agents, vinca alkaloids, antimetabolites etc. Many different single-agent treatments are in use for patients who have received prior treatment with an alkylating agent, an anthracycline, and rituximab, individually or in combination. Currently no single-agent treatment is consistently used or considered superior for the treatment of relapsed MCL.

Non-Clinical aspects

N/A

Clinical aspects

GCP compliance

According to the MAH all studies were conducted in accordance with the ethical requirements of Directive 2001/20/EC and with the ICH E6 guideline on Good Clinical Practice and the principles set forth in the Declaration of Helsinki.

- Clinical Pharmacology

Pharmacokinetics

Introduction

In support of this application for the use of temsirolimus IV in patients with MCL, an integrated population PK analysis of temsirolimus was provided in CSR-70829. The analysis combined PK data obtained from studies 3066K1-124-US, -145-US, -200-US, -203-EU (all previously submitted for the RCC marketing authorisation application (MAA)) and the pivotal MCL study -305-WW, and included

temsirolimus and from 1648 samples from 279 subjects for sirolimus. The MCL population represented 40% and 24.2% of the total subjects in the population PK datasets for temsirolimus and sirolimus, respectively, and the blood sampling typically spanned study weeks 3 to 6.
Furthermore, an additional completed phase 1/2 dose-escalation study of temsirolimus in combination with sunitinib (study 3066K1-402-WW), and an updated progress report on safety in 1 ongoing study in paediatric patients (study 3066K1-139-US) was provided (see Table 8). A progress report for 1 additional ongoing study in subjects with cancer who had hepatic impairment (NCI protocol 6813, Wyeth study 3066K1-152-US) was previously provided in support of the RCC MAA.

In vitro studies have demonstrated that single-agent temsirolimus exhibits important antitumour activity. Sirolimus, which is a major metabolite of temsirolimus following IV treatment, was also shown to have antitumour activity. The appearance of appreciable levels of sirolimus in the circulation of subjects with cancer therefore provided a rationale to derive a composite metric of drug exposure that described the algebraic sum of the areas under the concentration-time curve (AUC_{sum}) for both entities. Although temsirolimus and sirolimus share some common biological properties, substantial differences in the profile of activity and side effects can be obtained with differences in dose level, dose schedule, or route of administration.

The proposed treatment regimen for patients with MCL is 175 mg IV weekly for 3 weeks followed by weekly 75-mg IV doses. The comparative PK parameters described below were determined using the typical values and variance terms for clearance and volume of distribution terms from the integrated population PK analysis. Since blood sampling in the subjects with MCL was sparse in nature, data pooling of PK values was not performed.

Methods

- **Analytical methods**

Temsirolimus and its major metabolite sirolimus were assayed in blood and plasma using a combined HPLC/MS/MS assay in which both temsirolimus and sirolimus were simultaneously measured. This assay was split into 2 methods to quantify 2 differing concentration ranges (i.e., low range 0.25-25 ng/ml, and high range 2.5-2500 ng/ml). A cross-validation of this combined method with the previous separate temsirolimus and sirolimus assays, which were used for earlier PK studies, was conducted. The methods were sufficiently validated. Accuracy (% bias) and precision (% coefficient of variation) were reported at low, mid and high QC levels, and were within generally accepted ranges.

- **Pharmacokinetic data analysis**

Population PK analysis
Pharmacokinetic data from the final models of the previous mechanistic integrated analysis (CSR-64107) were merged with data from subjects with MCL (Study 3066K1-305-WW) in Study CSR-70829. Studies included in the population PK analysis CSR-70829 are presented in Table 1.

Table 1: Studies included in population PK analysis CSR-70829

Study Number	Study Description	Number Enrolled	IV Dose Range
Clinical Pharmacology Studies in Healthy Subjects			
3066K1-145-US[a]	Phase 1, open-label study to quantify the temsirolimus exposure/response relationship using S6 ribosomal protein in blood.	30	1 to 25 mg
Clinical Studies with a Clinical Pharmacology Component in Subjects with Cancer			
3066K1-124-US[a]	Phase 1, open-label, dose-escalation combination study with IFN to determine MTD in subjects with advanced RCC.	71	5 to 25 mg
3066K1-200-US[a]	Phase 2, randomized, blinded, parallel-group, dose-ranging study for efficacy, safety, and population PK in subjects with advanced RCC.	111	25, 75, 250 mg
3066K1-203-EU[a]	Phase 2, randomized, open-label, parallel-group, dose-ranging study to evaluate efficacy, safety, and population PK in subjects with advanced or metastatic breast cancer.	109	75, 250 mg
3066K1-305-WW	Phase 3, randomized, open-label, parallel-group, pivotal study to evaluate efficacy and safety in subjects with relapsed or refractory MCL.	162	175 and 75 mg, 175 and 25 mg

[a] Final data were presented in the previous MAA for RCC. Data from these studies are included in population PK analyses in this MAA.

A summary of the comparison of the previous CSR-64107 and current population CSR-70829 PK data set is provided in Table 2.

Table 2: Comparison of the number of subjects and observations included in integrated population PK analyses CSR-64107 and CSR-70829

		N		
Analyte	Subgroup	Integrated analysis from CSR-64107	Integrated analysis CSR-70829, with data from Study 305	Change (%)
Temsirolimus	Subjects	90	150	+67%
	Observations	1153	1342	+16%
Sirolimus	Subjects	211	279	+32%
	Observations	1312	1648	+25%

For the temsirolimus model, a nonlinear structure to describe both plasma and whole blood disposition, based on Study 3066K1-145-US of temsirolimus with healthy subjects, was applied. This model utilized 4 compartments in which specific, saturable distribution of temsirolimus to 2 of 3 peripheral compartments (blood cells and peripheral tissue) was described. The linear, 2-compartment model with first-order formation was applied to characterize sirolimus concentrations in blood. The same mechanistic model was used in current CSR-70829 as in the previous CSR-64107 (Figure 1). The final model for temsirolimus was based a data set of 1342 observations for 150 subjects.

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