

Annex I

**Scientific conclusions and grounds for maintenance of marketing
authorisation presented by the European Medicines Agency**

Scientific conclusions

Overall summary of the scientific evaluation of Temodal

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. Other Cetero Research sites were not affected.

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

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 Temodal, 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product and specifically on whether the marketing authorisation for Temodal should be maintained, varied, suspended or withdrawn.

Temodal contains temozolomide (TMZ), a nearly 100% orally available pro-drug of monomethyl triazenoimidazole carboxamide (MTIC), an alkylating agent related to dacarbazine and procarbazine. Temodal is authorised via the centralised procedure and all formulations and strengths are indicated in the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as mono-therapy treatment as well as in children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. Temodal is available as 5 mg, 20 mg, 100 mg and 250 mg hard capsules (first authorised on 26th January 1999) and as 140 mg and 180 mg hard capsules (authorised on 23rd April 2007). Temodal is also authorised as a 2.5 mg/ml powder for solution for infusion (authorised on 17th February 2009), for patients with brain tumours unable to swallow the oral formulation. Dose recommendations for the oral and the intravenous (IV) formulations are identical and based on mg per sqm of body surface area).

The MAH stated that the two pivotal studies supporting the line extension EMEA/H/C/229/X/35 which granted the additional powder for infusion formulations were study P02466 "*A Pilot Comparative Bioavailability Study of Oral and Intravenously Administered Temozolomide in Patients With Primary CNS Malignancies*" (initiated on 10th December 2004 and completed on 30th August 2005) and study P02467 "*A Bioequivalence Trial of Oral and Intravenously Administered Temozolomide in Patients with Primary CNS Malignancies*" (initiated on 29th September 2006 and completed on 18th October 2007). The scope of both trials was to show a 100% oral bioavailability of the capsules and consequently implement identical posology for the capsules and the powder for infusion for each individual indication respectively. Both studies were analysed by Cetero Research during the identified period of concern.

The MAH provided responses to the CHMP list of questions by stating that in January 2006, it received scientific advice from the Committee for Medicinal Products for Human Use (CHMP) regarding the registration of the intravenous formulation of temozolomide (TMZ) and specifically for its clinical development. The CHMP agreed that since the oral bioavailability of TMZ is close to 100%, a bridging program to the oral formulation was sufficient to support the IV registration. In particular, a clinical program was designed to establish the pharmacokinetic profiles of TMZ and MTIC obtained with IV administration compared to those obtained with oral administration.

In study C95-006 (not conducted or analysed by Cetero Research and submitted within the initial application for the oral formulation) which investigated the absorption, metabolism and excretion of orally administered ¹⁴C radiolabelled TMZ in humans, less than 1% of the dose was recovered in faeces, demonstrating that more than 99% of the dose was absorbed. The IV dose, because it bypasses the absorptive process, would by definition be completely absorbed. Additionally, prior to the development of Temodal the Cancer Research Campaign independently conducted an absolute bioavailability study using a capsule formulation of TMZ and intravenously administered TMZ, and the mean (n=5 patients) oral bioavailability was calculated as 109%. The MAH also referred to

preclinical studies submitted in the initial application for the oral formulation, which demonstrated complete (95 to 100%) bioavailability of TMZ when administered orally to rats (studies P-5864 and P-6097) and beagle dogs (studies P-5892 and P-6098). The MAH considered that collectively, this data confirms the complete bioavailability of the oral formulation in humans, independently of the evidence obtained from studies analysed by Cetero Research. The MAH therefore considered there to be little further clinical value in re-determining the exact bioavailability of the two formulations in order to establish bioequivalence between the oral and IV formulations of TMZ.

As further evidence that the oral and IV formulations of TMZ result in equivalent exposure, the MAH resubmitted some additional modelling and simulation analyses, demonstrating similar exposure following administration of the IV and oral formulation. These analyses, which did not involve Cetero Research, were submitted in the original IV line extension application. The first analysis assessed the feasibility of the bioequivalence strategy of oral and IV TMZ, while the second simulated cross-over bioequivalence study designs between the PO and IV formulations. The simulations showed that a bioequivalence study comparing oral TMZ administration to a 1.5 hour IV infusion would have a probability of over 90% of successfully showing bioequivalence. The MAH considered that these simulations support the bioequivalence of the IV and oral formulations.

Finally, the MAH stated that based on experience acquired from the original bioequivalence study, enrolment in a repeated bioequivalence study will be difficult and completion is estimated to take over 2 years. The MAH considered that conducting such a trial would also present hardships to patient who can take oral TMZ and therefore have no reason to take IV and to patients who cannot take oral TMZ, and hence need the IV. The MAH therefore considered that participation in a new bioequivalence study would provide no benefit to patients who require the IV formulation and would serve as an inconvenience and potential risk to subjects who are able to take oral TMZ.

In conclusion, the MAH did not consider that the concerns raised regarding the bio-analytical analyses conducted at the Cetero Research facilities in Houston affect the validity of the line extension to the IV formulation, as the nearly 100% bioavailability of oral TMZ and the bioequivalence of the oral and IV TMZ formulations is supported by scientific results from independent studies not conducted by Cetero Research, as supported by the modelling and simulation information. In addition, the concerns associated with conducting a repeat study support the proposal not to repeat a bioequivalence study.

The CHMP, having carried out an initial assessment of the findings of the inspection of the Cetero Research facilities, concluded that these did not impact the benefit-risk of the oral formulations and that only IV formulations were potentially affected.

The CHMP noted the scientific advice received by the MAH in 2006, in the context of a line extension to introduce an intravenous formulation, stated that a bioequivalence trial was required in order to waive the requirement of a confirmatory and comparative (oral vs. intravenous) phase III clinical trial. The MAH complied with this requirement by conducting the studies P02466 and P02467. However, considering the uncertainties raised by the potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities, the CHMP assessed the MAH arguments and data to determine whether a nearly complete oral bioavailability allows to conclude on the bioequivalence of the IV formulation.

The CHMP noted that the absolute oral bioavailability of temozolomide is excellent, or near 100%, in several species other than humans. It was also noted that trial C95-006, which was not analysed by Cetero Research provides strong evidence that oral bioavailability is close to 100%, as currently stated in Section 5.2 of the Temodal SmPC. The simulation of the bioequivalence trial submitted by the MAH suggests that absorption after oral administration is rapid and complete and shows c_{max} and AUC values very similar to those obtained with intravenous administration. In addition, the result of the published trial 'Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies' (Brada et al, 1999), suggests both a 100% bioavailability and a bioequivalent behaviour of oral and intravenous temozolomide. In conclusion, the CHMP therefore considered rapid and "nearly complete" oral bioavailability of temozolomide to be well-established and also agreed that the bioavailability of oral temozolomide has been indirectly shown to be close to 100% in trials other than the questioned studies P02466 and P02467.

Overall conclusion

In conclusion, given the rapid and nearly complete oral bioavailability of temozolomide, established independently from analyses performed by Cetero Research, as well as the lack of any safety signal for the powder for solution for infusion, the CHMP considered it highly unlikely that the absence of

exact data on the actual oral bioavailability of temozolomide would raise safety concerns with regard to the current posology of the powder for solution for infusion. The CHMP considered the bioequivalent behaviour of intravenous and oral Temodal to be sufficient to support the waiving of performing a further oral bioavailability trial, or a formal bioequivalence trial and therefore concluded that the concerns raised regarding the bio-analytical analyses conducted at the Cetero Research facilities in Houston did not impact the efficacy and safety of the intravenous Temodal formulation, despite the doubts regarding the reliability of studies P02467 and P02466. As a consequence, the CHMP was of the opinion that the findings of the inspection of the Cetero Research facilities in Houston (Texas, USA) did not impact the benefit-risk balance of any of the authorised Temodal formulations.

Grounds for the maintenance of the marketing authorisation

- Whereas,
- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Temodal, initiated by the European Commission.
- The Committee reviewed the relevant available data.
- The Committee concluded, in view of available data, in particular evidence of a rapid and nearly complete oral bioavailability of temozolomide, that any potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities do not impact the benefit-risk balance of Temodal.
- The Committee, as a consequence, concluded that the benefit-risk balance of Temodal remains positive under normal conditions of use.