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EMA/14583/2013
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Tygacil

tigecycline

**Procedure number:** EMEA/H/C/000644/A-20/0072

## Note

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

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# 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. Other Cetero Research sites were not affected.

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

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 Tygacil provided responses in March 2012 and May 2012.

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 6 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 Tygacil, 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 Tygacil should be maintained, varied, suspended or withdrawn

# 2. Scientific discussion

Tygacil contains tigecycline, a glycylcycline antibiotic and an analogue of the semi-synthetic tetracycline, minocycline. Tygacil is authorised via the centralized procedure since 24th April 2006 and is currently approved in complicated skin and soft tissue infections, excluding diabetic foot infections and in complicated intra-abdominal infections. An application to extend the indications to include the treatment of community acquired pneumonia was withdrawn by the holder in April 2008 before the CHMP had reached an opinion. Tygacil is available as a powder for solution for infusion.

## *2.1. Clinical aspects*

The MAH provided responses to the CHMP list of questions, submitting an overview of the studies affected by the findings of the inspection of the Cetero Research facilities in Houston, Texas. A total of ten affected studies were identified for Tygacil and the MAH stated that a data examination and verification process has been initiated for all studies and is currently ongoing.

The MAH considered six of the identified studies to be irrelevant to the assessment of the impact of the findings of the inspection of the Cetero Research facilities on the benefit-risk balance of Tygacil. Studies 3074K5-319-WW, 3074A1-311-WW and 3074A1-313-WW were submitted in support of applications for indications (diabetic foot, nosocomial pneumonia and community acquired pneumonia respectively) which were subsequently withdrawn for Tygacil, while studies 3074A1-307-WW and 3074A1-308-WW did not support any indications or recommendation in the SmPC. The last study, study 3074A1-110-US, was an additional single dose study to characterize the pharmacokinetics of intravenous tigecycline in children, submitted as part of a failed application, in which the CHMP concluded that the submitted evidence in support of the dose regimen was weak and needed more investigation. As a consequence, the MAH performed study 3074A1-2207-WW (discussed later in the

report), which supersedes study 3074A1-110-US. No revised bioanalytical reports are available for these studies, but they are expected to become available in June 2013.

Regarding the four studies which were considered relevant, the MAH stated that revised bioanalytical reports were received from Cetero Research in April 2012 for these studies and provided summaries of the studies and the findings of the revised reports.

For study 3074A1-309-WW (*"A Phase 3, Open-Label, Non-comparative Study Of Tigecycline For The Treatment Of Subjects With Selected Serious Infections Due To Resistant Gram-Negative Organisms Such As Enterobacter Species, Acinetobacter Baumannii, And Klebsiella Pneumoniae"*), data from run 3 (of a total of 11) required recalculation of the regression equation. The run did not pass acceptance criteria, the results were removed and the report revised and reissued. A total of 9 serum concentrations were removed from a total of 160 samples. The MAH stated that these were critical samples as they were collected immediately after the infusion was completed and it will therefore be difficult to calculate the individual parameters using non-compartmental methods because of the limited number of samples collected for each subject. The MAH proposed to recalculate a summary of the remaining pharmacokinetic parameters and revise and submit the clinical study report to the CHMP when it becomes available, which is expected to be in June 2013.

For study 3074A1-2207-WW ("*A Multicenter, Open-Label, Ascending Multiple-Dose Study To Assess The Pharmacokinetics, Safety, And Tolerability Of Tigecycline In Patients 8 To 11 Years Of Age With Selected Serious Infections*"), data from 12 runs are valid as there was no evidence of sample substitution but data from the 13$^{th}$ run needs to be removed. The results for 3 subjects (#65, #173 and #178), all of whom received 1 mg/kg, had to be removed entirely. In this study, serum concentrations were measured to describe tigecycline pharmacokinetics in paediatric patients with complicated skin and skin structure infections, complicated intra-abdominal infections or community acquired pneumonia. The MAH provided the recalculation of the summary of the parameters presented in the SmPC, which resulted in minor changes to the pharmacokinetics data reported for a multiple dose study conducted in 8 – 11 year old patients, corresponding to an increase of 0.6% for Cmax and ~ 0.3% for AUC0-12h, which the MAH considered relatively modest. The MAH therefore concluded that the changes do not impact the overall conclusions and descriptive interpretation of the PK parameters observed in this age group. The MAH proposed to revise and submit the clinical study report to the CHMP when it becomes available, which is expected to be by end of February 2013.

For study 3074A1-120-US ("*Open-Label, Single-Dose Study of the Pharmacokinetics of Tigecycline in Adult Subjects with Primary Biliary Cirrhosis*"), a total of 3 serum sample results were removed (Subject 1, Period 1, hour 0.5 and Subject 26, Period 1, hours 48 and 96. Only the first result, which corresponds to the peak concentration for Subject 1, required reanalysis of the pharmacokinetic parameter, as the other results were previously reported as below the quantitation limit (BQL). The MAH proposed to recalculate the pharmacokinetic parameters as possible, determine the summary statistics and revise and submit the clinical study report to the CHMP when it becomes available, which is expected to be in June 2013.

Study 3074A1-119-US ("*Open-Label, Multiple-Dose Study of the Pharmacokinetics of Tigecycline in Human Bone*") was never submitted to the CHMP. The bone assay was not performed by Cetero Research and was not in question. A single serum concentration (Subject 18, Period 1, Day 2, Hour 1) needed to be removed. The corresponding bone sample was not collected properly, so the bone:serum ratio was not reported. The serum concentration was combined with those collected at the same time from 7 other subjects. Redacting the single concentration caused a 2% decrease in the reported the average concentration for the time but no change in the reported AUC for serum and consequently, no change in the ratio of AUCbone:AUCserum was reported for the study. The MAH proposed to revise and submit the clinical study report to the CHMP when it becomes available, which is expected to be in June 2013.

The CHMP noted the four studies considered critical due to the potential impact of the concerns raised regarding the bio-analytical analyses conducted at the Cetero Research facilities in Houston.
The CHMP acknowledged that study 3074A1-119-US was never submitted to the CHMP.
Study 3074A1-309-WW was an open-label, non-comparative, multicentre study to evaluate the safety and efficacy of tigecycline in subjects with selected serious infections caused by resistant gram-negative organisms. It was submitted as part of the original Tygacil marketing authorisation application but no statements regarding the efficacy of tigecycline in this study population is included in the SmPC and the CHMP therefore considered that the ongoing re-analysis will not have an impact on the Tygacil marketing authorisation.

Study 3074A1-120-US was submitted in the context of the follow-up measure FU2 021.2, to assess the pharmacokinetics profile of tigecycline in patients with biliar cholestasis. The information provided in this study did not modify the CHMP concern on the potential risk for overexposure in patients with biliar cholestasis, since the data presented was very limited and generated only in patients with minor degrees of cholestasis. As a result, no SmPC modifications were implemented and the CHMP was therefore of the opinion that the results of the reanalysis of samples will impact neither the conclusions of the study not the Tygacil marketing authorisation.

Study 3074A1-2207-WW was submitted to support variation EMEA/H/C/644/II/057 to include paediatric pharmacokinetic data in section 5.2 of the SmPC, as requested by the CHMP in FUM 52.1. It is the only study considered to have a possible impact on the marketing authorisation of Tygacil, as data from this study are referenced in the Tygacil SmPC. The CHMP agreed with the MAH position that only a few data are affected and that once corrected, there will only be a need for a small revision of the information available, given that the revised data will represent a change of less than 1% and will not impact the understanding of the pharmacokinetics of tigecycline in children. Considering that no indication or posology recommendation for the paediatric population is given in section 4.2 of the SmPC and bearing in mind the preliminary findings and reanalyses conducted, the possible impact is expected to be minimal. The CHMP was therefore of the view that the SmPC should be updated to reflect the revised PK data in children, once the results of the ongoing third party audit become available.

Regarding the 6 other studies potentially affected, the CHMP agreed that these are not considered critical and was of the view that there is no need for specific action. The CHMP noted that the MAH will present final reports for all ten studies after the conclusions of the ongoing investigations, which is considered sufficient.

# 3. Overall discussion and benefit/risk assessment

In conclusion, having assessed the responses provided by the MAH with regard to the studies affected by the findings of the inspection of the Cetero Research facilities in Houston (Texas, USA), the CHMP was of the view that the concerns raised regarding the bio-analytical analyses conducted at the Cetero Research facilities in Houston (Texas, USA) did not impact the efficacy and safety of Tygacil and that the benefit-risk balance therefore remains positive.

# 4. Conclusion and grounds for the recommendation

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Tygacil, initiated by the European Commission.
- The Committee reviewed the relevant available data.
- 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 the benefit-risk balance of Tygacil.

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