EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/41126/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC

Tibolona Aristo and associated names
Tibocina and associated names

INN of the active substance: tibolone

Procedure no: EMEA/H/A-29/1389
EMEA/H/A-29/1390

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

1.1. Decentralised procedure (DCP) and CMDh 60 day procedure

Aristo Pharma GmbH submitted applications under the decentralised procedure for Tibolona Aristo and associated names and Tibocina and associated names, 2.5 mg tablets on 11 September 2012.

The application was submitted to the reference Member State (RMS): Spain and the concerned Member States (CMS): Germany for ES/H/0223/001/DC and Belgium, Germany and The Netherlands for ES/H/0224/001/DC.

The Decentralised procedure ES/H/0223-0224/001/DC started on 10 October 2012.

On day 210, Germany considered that major issues on bioequivalence remained unsolved; hence the procedure was referred to the CMDh, under Article 29, paragraph 1 of Directive 2001/83/EC by Spain on 5 August 2013. The CMDh 60 day procedure was initiated on 2 September 2013

Day 60 of the CMDh procedure was on 31 October 2013 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by Spain on 31 October 2013. Germany raised public health objections regarding the demonstration of bioequivalence.

2. Scientific discussion during the referral procedure

2.1. Introduction

Tibolone is a synthetic steroid hormone drug which acts as an agonist, mainly on oestrogen receptors. Two applications under the decentralised procedure were submitted by Aristo Pharma GmbH, for the generic products Tibolona Aristo and Tibocina, both 2.5 mg tablets with the indication “treatment of oestrogen deficiency symptoms in women, more than one year after the menopause”, which is the same as that of the reference product.

A single bioequivalence study (a mono-centre, open, randomised, single dose, four-period, replicate crossover trial in postmenopausal women to evaluate the bioequivalence of two oral preparations containing 2.5 mg tibolone) was conducted to support both applications. Following the assessment of the application dossiers by the reference member state (RMS), both applications were considered approvable based on the quality, non-clinical and clinical data presented. However, a Good Clinical Practice (GCP) inspection of the clinical facility in Sofia, Bulgaria carried out during the procedure, on 18-19 June 2013, identified a lack of evidence documenting the transfer date and time and the identification of pharmacokinetic (PK) samples from the dry ice box used for flash freezing to the freezer used at this site until the samples were transferred to the bioanalytical site in Barcelona, Spain. In addition, the inspection was unable to confirm whether any further movement of these samples had occurred. These findings were classified as critical from an inspection point of view and one of the concerned member states therefore considered that the findings of the GCP inspection made it impossible to conclude on the reliability of the bioequivalence study. A referral under Article 29(4) of Directive 2001/83/EC was therefore triggered and the CHMP was requested to give its opinion on whether the proposed products Tibolona Aristo and Tibocina can be considered bioequivalent to the reference product.

2.2. Critical evaluation

The CHMP agreed that no evidence of adequate transfer and storage of the study PK samples at the clinical site was provided for a period of 75 days (date of first blood collection until last date of shipment to analytical site). In addition, no documentation was made available regarding to re-identification of study samples when transferred from the dry ice box into the freezer and no documentation on the equipment (freezer) where samples were stored or the storage conditions. The CHMP acknowledged that with regard to GCP compliance, these findings must be considered as a critical deficiency. Maintaining PK samples under adequate temperature conditions is of importance in the case of a bioequivalence trial, particularly for a generic application and the CHMP agreed that there is a reasonable doubt about the appropriateness of this process given the absence of documentation, as stated in the inspection report, with the potential consequence that the quality and integrity of the data might have been adversely affected and that these concerns of inadequate storage conditions could potentially result in decreased plasma concentrations of the active substance.

However, the CHMP did not consider that GCP inspection findings classified as critical should automatically invalidate the results of a bioequivalence study and instead considered that such decisions should be taken on a case by case basis following a careful evaluation of the findings and their potential impact on the rights, safety or wellbeing of the subjects and/or the quality and integrity of data, as per the definitions stated in the Procedure for reporting of GCP inspections requested by the CHMP, EMA/INS/GCP/588734/2012. The CHMP therefore reviewed the additional clinical evidence available, including the assessment carried out during the CMDh procedure and the evidence submitted to the CMDh by the Applicant to support their view that adequate sample identification and registration had taken place.

The CHMP noted that the Applicant submitted a summary of the entire study samples management process, from the time of sampling to the analysis of the samples, including a description of the methods used to identify study participants and to label and record the samples obtained, although it was acknowledged that this documentation had not been submitted during the inspection procedure and instead only during the CMDh referral procedure.

Following collection and processing, the samples were flash-frozen in a dry ice cooling container and the time point was documented in the ‘flash freezing log’. Each batch of samples collected during each respective study day was added to the dry ice box during the study day. At the end of each day, the contents of this dry ice box were immediately (within a minute) transferred to the -80°C freezer, as documented in the protocol for return of dry ice. Due to the number of samples, and in order to avoid unnecessary exposure of samples to room temperature, a re-identification of individual samples while moving them into the freezer was deliberately not performed keeping in mind that the information regarding the individual identification of each sample was already captured in the sampling, centrifugation, and flash-freezing logs as well as on the sample labels. The freezer used for long-term storage in the study was identified including its model, manufacturer and serial number on the list of equipment used at the site and the freezer was locked with only the principal investigator or persons authorised having access to the key. A dedicated data logger continuously monitored the temperature in the freezer. At the end of the study, the samples were immediately transferred from the freezer to the dry ice shipment box together with a temperature logger for the transport. The serial numbers of the loggers used are documented on the biological sample shipment record. The temperature curves of all loggers used were controlled at the contract research organisation and also provided to the analytical facility before analysis. No deviations were observed with regard to the temperature records obtained. As the temperature loggers for the transport boxes were placed in the respective boxes together with the samples, the exact time point of packing the samples for transport can be derived from the respective temperature logs and information on the exact time point at which the samples

were retrieved from the freezer to be shipped to the analytical laboratory is therefore available. On arrival at the analytical facility, the condition of the bulk of samples was checked and recorded on the 'biological sample shipment record' before they were transferred to the analytical facilities' -80°C freezer. In this step, the analytical site confirmed that the arriving samples were properly identified by the Clinical Unit and no deviations were reported. At extraction time, when samples are thawed for analysis, each separate sample was again individually identified and no deviations were reported for this bioequivalence study. Finally, the storage conditions at the analytical site were documented using continuous temperature monitoring by means of a data logger for the entire period of storage, from receipt of the first sample shipment to the destruction of last samples.

Having reviewed the available data, the CHMP considered that in the specific case of the two generic applications under discussion, there was sufficient additional evidence which indicated that the study PK samples were not put at risk during the study and that these were maintained under adequate temperature conditions. In addition, the bioequivalence study conducted demonstrated bioequivalence, with observed drug concentrations (both for C_{max} and for AUC) being comparable or superior to those reported in the literature and the CHMP considered that these results suggest that no significant degree of drug degradation occurred.

The CHMP therefore concluded that while notable deviations from GCP requirements were identified during the conduct of the bioequivalence study, the totality of the available evidence confirms that the results of the bioequivalence study are reliable and demonstrates the bioequivalence of the proposed products and the reference product.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

The CHMP considered the bioequivalence of the proposed products to the reference product to be demonstrated and therefore recommended that the marketing authorisations for Tibolona Aristo and associated names and Tibocina and associated names be granted.

2.5. Conclusions and benefit-risk assessment

Based on:

- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit-risk ratio of Tibolona Aristo and associated names and Tibocina and associated names is considered to be favourable. The CHMP issued positive opinions recommending the granting of the marketing authorisations and the agreement of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.

The divergent positions are appended to the CHMP opinion.

Appendix 1

Divergent positions to CHMP opinion

Article 29(4) referral of Council Directive 2001/83/EC

Procedure No: EMEA/H/A-29/1389
EMEA/H/A-29/1390

Tibolona Aristo and associated names
Tibocina and associated names

Divergent statement

Based on the presented evidence in their totality, we are of the following opinion:

During a GCP inspection it was found that storage and transfer conditions of the plasma samples from the pivotal bioequivalence study were not traceable for a period of up to 75 days. This was considered as a critical GCP violation. In addition, transient decreases of tibolone plasma concentrations were observed frequently. Transient decreases are compatible with and possibly caused by decreased stability of tibolone in plasma samples, due to insufficient storage conditions. Therefore, the tibolone plasma concentrations measured in this study are not considered as reliable. Following the GCP inspectorate´s recommendation, the data should not be used for evaluation of bioequivalence between the proposed products and the reference product.

Therefore, bioequivalence between Tibolona Aristo and Tibocina and their reference product cannot be concluded and a Marketing Authorization for Tibolona Aristo and Tibocina should not be granted.

CHMP members expressing a divergent opinion:

Daniel Brasseur	18 December 2013	Signature: ……...
David Lyons	18 December 2013	Signature: ……...
Aikaterini Moraiti	18 December 2013	Signature: ……...
Ondřej Slanař	18 December 2013	Signature: ……...
Jan Mueller-Berghaus	18 December 2013	Signature: ……...
Outi Mäki-Ikola	18 December 2013	Signature: ……...
Andrea Laslop	18 December 2013	Signature: ……...
Ivana Mikačić	18 December 2013	Signature: ……...

Jean-Louis Robert	18 December 2013	Signature: ……...
Harald Enzmann	18 December 2013	Signature: ……...
Alar Irs	18 December 2013	Signature: ……...
Jacqueline Genoux-Hames	18 December 2013	Signature: ……...

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Tibocina and associated names

Divergent statement

Based on the presented evidence in their totality, I am of the following opinion:

During a GCP inspection it was found that storage and transfer conditions of the plasma samples from the pivotal bioequivalence study were not traceable for a period of up to 75 days. This was considered as a critical GCP violation. In addition, transient decreases of tibolone plasma concentrations were observed frequently. Transient decreases are compatible with and possibly caused by decreased stability of tibolone in plasma samples, due to insufficient storage conditions. Therefore, the tibolone plasma concentrations measured in this study are not considered as reliable. Following the GCP inspectorate´s recommendation, the data should not be used for evaluation of bioequivalence between the proposed products and the reference product.

Therefore, bioequivalence between Tibolona Aristo and Tibocina and their reference product cannot be concluded and a Marketing Authorization for Tibolona Aristo and Tibocina should not be granted.

CHMP member expressing a divergent opinion:

Karsten Bruins Slot	18 December 2013	Signature: ……...
Kolbeinn Gudmundsson	18 December 2013	Signature: ……...