01 October 2012
EMA/561829/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Conbriza

bazedoxifene

Procedure number: EMEA/H/C/000913/A20/0025

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.

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

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 Conbriza 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 Conbriza, 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 Conbriza should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Conbriza (bazedoxifene) is a non-steroidal selective oestrogen receptor modulator (SERM) that exhibits oestrogen receptor tissue selective agonist activity on the skeletal system and lipid metabolism, as well as oestrogen antagonist activity in breast and uterine tissue. Conbriza received a Marketing Authorisation in the European Union (EU) in April 2009.

Study 3068A1-131-US entitled 'the effects of bazedoxifene acetate on cardiac repolarization' was a QTc study of bazedoxifene acetate where part of the analysis was conducted by the concerned laboratory Cetero research.

2.1. Clinical aspects

Study 3068A1-131-US

Study 3068A1-131-US investigated the effects of bazedoxifene on cardiac repolarization.

Participants in the study received either bazedoxifene acetate or moxifloxacin as a positive control.

The analytical run for moxifloxacin was performed between 9 and 11 of February 2006 by BA Research International (Houston, Texas), now part of Cetero.

Plasma concentrations of bazedoxifene were analysed by a different laboratory. Therefore any potential impact will be restricted to the plasma concentrations of the positive control moxifloxacin, and while assay sensitivity can be questioned, the conclusions of the study with regards to bazedoxifene will not be significantly impacted.

Additional data on QT prolongation

The efficacy and safety data supporting the marketing authorisation application were mainly based on:

- The multicentre, double-blind, randomized, placebo- and raloxifene-controlled, phase 3 study 3068A1-300-GL in postmenopausal women for the prevention of osteoporosis
- And the 36-month, multicentre, double-blind, randomized, placebo- and raloxifene-controlled, phase 3 study 3068A1-301-WW in older, postmenopausal women for the treatment of osteoporosis.

The 3-year Core study of 301-WW (CSR-39808) was extended by two 2-year double-blind, placebo-controlled study extensions to assess the long-term efficacy and safety of bazedoxifene in the reduction in fracture incidence in postmenopausal women with osteoporosis.

The pivotal phase 3 trial 3068A1-301-WW in older, postmenopausal women for the treatment of osteoporosis included a placebo arm as well as the active comparator raloxifene. Four-hundred and three (403) subjects participated in a ECG substudy, 399 of whom were evaluable. This substudy included an assessment of the potential of bazedoxifene for prolongation of the QT interval, a screening/baseline ECG was obtained and triplicate ECGs were recorded while on therapy. None of the subjects in the ECG substudy had clinically relevant signs or symptoms of arrhythmias related to QT interval prolongation, and QT interval prolongation was not reported as an adverse event for any of these subjects. No subjects in the ECG substudy population were withdrawn from the study because of QT prolongation. Safety data from this trial are available from the 3-year core study as well as the two 2-year double-blind extension studies. Neither these data nor available post-marketing data indicate a relevant effect of bazedoxifene on cardiac repolarisation.

In addition, from available preclinical *in-vitro* and *in-vivo* data bazedoxifene is highly unlikely to exhibit relevant effects on heart rate and blood pressure. It was demonstrated that exposure to the metabolites was significantly higher in the cardiovascular safety studies conducted in monkeys as compared to humans (> 4.9 times). Therefore, bazedoxifene and its metabolites are not likely to affect the cardiac function at the therapeutic concentrations.

Based on these data it can be concluded that the benefit-risk ratio remains unchanged even if the results of study 3068A1-131-US regarding moxifloxacin would have been falsified.

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.

In study 3068A1-131-US, only the plasma concentrations of the positive control moxifloxacin were analysed by Cetero. As plasma concentrations of bazedoxifene 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 Conbriza.

4. Conclusion and grounds for the recommendation

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Conbriza, 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 Conbriza.

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