31 January 2019
EMA/CHMP/41310/2019

CHMP List of questions

To be addressed by the marketing authorisation holder for Lartruvo

Procedure under Article 20 of Regulation (EC) No 726/2004

Lartruvo EMEA/H/A-20/1479/C/4216/015

Marketing authorisation holder(s): Eli Lilly Nederland B.V.

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1. Background

Lartruvo was granted a conditional marketing authorisation under Article 14(7) of Regulation (EC) No. 726/2004, valid throughout the European Union, on 9 November 2016. The therapeutic indication of Lartruvo is:

'in combination with doxorubicin, for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin'.

Lartruvo was authorised based on a single open-label, randomised phase 1b/2 clinical trial which enrolled doxorubicin-naïve subjects with advanced soft tissue sarcoma not amenable to treatment with surgery and radiotherapy (study JGDG). In this trial, treatment with olaratumab in combination with doxorubicin resulted in an improvement in progression-free survival (PFS) (8.2 vs. 4.4 months according to independent assessment; 6.6 vs. 4.1 months, hazard ratio (HR) 0.672 [95% CI: 0.442, 1.021], p = 0.0615 according to investigator assessment) and overall survival (OS) (26.5 months vs. 14.7 months, HR = 0.463; p = 0.0003).

In order to confirm the efficacy and safety of olaratumab, the marketing authorisation holder was required to submit, by January 2020, the clinical study report of a phase III randomised double-blind confirmatory study comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic soft tissue sarcoma (study JGDJ), including exploratory biomarker data. Study JGDJ completed enrolment in July 2016.

In January 2019, the marketing authorisation holder communicated to the European Medicines Agency high level preliminary results of the JGDJ study. In total, 509 patients were randomised to treatment either with Lartruvo + doxorubicin (followed by Lartruvo monotherapy until progression) or with placebo + doxorubicin (followed by placebo monotherapy until progression).

The study gives rise to concerns about lack of efficacy, because it did not meet the primary objective to prolong survival in the overall population (HR=1.05; median 20.4 vs. 19.7 months for Lartruvo + doxorubicin vs. placebo + doxorubicin) or in the leiomyosarcoma sub-population (N = 234, HR=0.95; median 21.6 vs. 21.9 months for Lartruvo + doxorubicin vs. placebo + doxorubicin). Furthermore, there was no clinical benefit in key secondary efficacy endpoints (progression-free survival in the overall population: HR=1.23, p = 0.042; median 5.42 months vs. 6.77 months for Lartruvo + doxorubicin vs. placebo + doxorubicin; overall response rate: 14.0% vs. 18.3% for Lartruvo + doxorubicin vs. placebo + doxorubicin).

2. Questions

The marketing authorisation holder (MAH) is requested to address the following questions:

1. The MAH is requested to submit the clinical study report of the study I5B-MC-JGDJ (ANNOUNCE).
2. The MAH should provide the following information on the MAH sponsored and not sponsored clinical trials with olaratumab:
    - Number of patients recruited and planned to be included in each completed and ongoing study.
    - Details about how the trial monitoring strategy in particular for efficacy concerns, considering the outcomes from ANNOUNCE study, is being carried out, and whether further actions should be implemented in clinical trials.
3. The MAH is requested to provide information on the current status of the PASS I5B-MC-B001 (observational study of olaratumab in combination with doxorubicin in patients with advanced soft tissue sarcoma in routine clinical practice), and to provide all available data from the study.
4. The MAH should provide the current marketing status worldwide.
5. In light of all the available data and taking into consideration the results from the study I5B-MC-JGDJ (ANNOUNCE), the MAH should explore and comment on the discrepancy between the results of the I5B-IE-JGDG (JGDG) study and of the ANNOUNCE trial, and discuss the benefit-risk balance of Lartruvo in the approved indication.