NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the CHMP made by the European Commission (EC):

Product(s) Name(s)	Lartruvo
Active substance(s) *Please clarify name(s)*	Olaratumab
Pharmaceutical form(s) *If all pharmaceutical forms are included, state "All".* *If not all pharmaceutical forms are included, please specify the one included.*	All
Strength(s) *If all strengths are included, state "All".* *If not all strengths are included, please specify the one included.*	All
Route(s) of Administration *If all routes of administration are included, state "All".* *If not all routes of administration are included, please specify the ones included.*	All
Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V.

Olaratumab is an antagonist of platelet derived growth factor receptor-α (PDGFR-α), expressed on tumour and stromal cells. Olaratumab is a targeted, recombinant, fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFR-α, blocking PDGF AA, -BB, and -CC binding and receptor activation. As a result, *in vitro* olaratumab inhibits PDGFR-α pathway signalling in tumour and stromal cells. In addition, *in vivo* olaratumab has been shown to disrupt the PDGFR-α pathway in tumour cells and inhibit tumour growth.

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 Ib/II 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.

On 17 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 endpoint 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). No explanation, such as related to pharmacokinetic exposures, treatment after progression or trial conduct, has been identified. No new safety concerns were identified, and the safety profile was comparable between treatment arms.

It is our understanding that dissemination of a Dear Healthcare Professional Communication on the results of this study has already been agreed to by CHMP, including a recommendation for no new patients to initiate treatment with Lartruvo. Additionally, the Agency has disseminated this recommendation in a public health communication.

In view of the above, the EC initiates a procedure under Article 20 of Regulation (EC) No. 726/2004 and requests the CHMP to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product Lartruvo (olaratumab). The EC requests the CHMP to give its opinion, as soon as possible and by 30 September 2019 at the latest, on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked, including whether provisional measures are necessary.

Signed [redacted] Date 25/01/2019.

Head of Unit - Medicines: policy, authorisation and monitoring
Directorate-General Health and Food Safety
European Commission