NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) No 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) No 726/2004 to the CHMP made by the European Commission (EC):

Product(s) Name(s)	Yondelis
Active substance(s) *Please clarify name(s)*	Trabectedin
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)	Pharma Mar S.A.

Yondelis is an anti-cancer medicinal product with two indications:

1. treatment of patients with advanced *soft-tissue sarcoma*, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents;
2. in combination with pegylated liposomal doxorubicin (PLD), Yondelis is indicated for the treatment of patients with relapsed platinum-sensitive *ovarian cancer*.

The marketing authorisation was issued on 17/09/2007 for the soft tissue sarcoma indication. The ovarian cancer indication was authorised in 2009 based mainly on OVA-301, a randomised, open-label, multicentre phase 3 trial to evaluate the efficacy and safety of trabectedin in combination with pegylated liposomal doxorubicin (PLD) in 645 patients with relapsed ovarian cancer (various number of lines of previous treatment). The trial showed superiority of trabectedin with PLD compared to PLD alone in terms of progression-free survival (PFS, primary endpoint): 21% risk reduction for disease progression (HR=0.79, CI: 0.65-0.96, p=0.02). Also, overall response rates were higher with trabectedin combined with PLD (27.6% vs 18.8% with PLD alone). Results for overall survival were compatible with a risk reduction for death with a 95% CI 0.72-1.02, but without significance. No additional studies on the ovarian cancer indication were requested of the MAH.

After the indication was authorised in the EU, trial OVC-3006 was started. It was a randomised, open-label, multicentre (Asia, US, 2 EU Member States) phase 3 study evaluating the efficacy and safety of trabectedin in combination with PLD in patients with platinum-sensitive, advanced, relapsed ovarian cancer who had received two previous lines of platinum-based chemotherapy, compared to PLD alone and with overall survival (OS) as primary endpoint.

Following a review of the results of a second interim analysis for futility, the Independent Data Monitoring Committee (IDMC) recommended on 15 December 2017 discontinuation of the study, due to lack of survival superiority in the trabectedin in combination with PLD arm over PLD alone arm. The study failed to achieve both the primary endpoint of OS and the secondary endpoint of PFS.

At time of discontinuation, a total of 576 patients were randomised, out of about 670 patients originally planned. The median overall survival for the trabectedin in combination with PLD arm was 23.8 months, compared with 22.2 months for the PLD arm (HR=0.93, 95% CI: 0.73-1.18; p=0.52), not indicating a difference in OS between treatment arms. In terms of key secondary endpoints, no difference between treatment groups was observed in PFS (HR=0.935, 95% CI: 0.762-1.147; p=0.5174), while the observed overall response rate was higher for trabectedin in combination with PLD (46%) than PLD alone (36%).

The MAH did not communicate the results of this study to the European Medicines Agency until November 2019, when they were included in a PSUR submission. In January 2020 during assessment of the PSUR, the MAH was requested to provide more information on the study and the reasons for its discontinuation. The preliminary assessment of this information make it clear that there are differences between OVA-301 and OVC-3006 with respect to major aspects of trial design and conduct (e.g. patient population, stratification, regions) that need to be assessed in detail. However, trial OVC-3006 enrolled certain patients with ovarian cancer who belong to the broader patient population with ovarian cancer for whom Yondelis is indicated. Therefore, the impact of trial OVC-3006 on the benefit-risk balance of Yondelis in the ovarian cancer indication needs to be assessed.

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 Yondelis (trabectedin). The EC requests the Agency to give its opinion by December 2020 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked. In addition, the EC requests the Agency to give its opinion as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of this medicinal product.

Signed [redacted] Date 21.02.2020
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General