14 June 2019
EMA/PRAC/317692/2019

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for leuprorelin-containing depot medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1486

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1. Background

This referral procedure concerns the leuprorelin-containing depot formulations. Leuprorelin is a gonadotropin releasing hormone (GnRH) agonist, which when used continuously leads to a decrease of gonadotrophin and sex steroid levels.

It is authorised in EU for the treatment of advanced hormone-dependent prostate cancer, breast cancer, endometriosis, symptomatic uterus myomatosus, uterine fibrosis, and precocious puberty. Leuprorelin-containing depot products have duration of action of 1, 3 or 6 months. The product presentations include implants as well as powders and solvents for the preparation of injections. Leuprorelin-containing products are injected subcutaneously or intramuscularly.

There have been reports for medication errors possibly leading to lack of efficacy with all leuprorelin-containing products. For one product (Eligard) there have been 2,271 cases of handling errors reported for the period from 01 January 2012 to 31 December 2018. In 120 cases, lack of efficacy associated with handling errors was reported.

As a consequence, on 07 June 2019, Germany notified PRAC on a referral under Article 31 of Directive 2001/83/EC for leuprorelin-containing products depot formulations in order to further characterise and mitigate the risk of medication errors and associated risk of lack of efficacy of leuprorelin-containing depot products.

In addition, the PRAC considered it necessary to perform a EudraVigilance analysis of reports of cases of medication errors with leuprorelin-containing products depot formulations. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EudraVigilance analysis will be provided to all MAHs together with the preliminary assessment reports.

2. Questions

The marketing authorisation holders (MAH) are requested to address the following questions:

Question 1

Please provide an overview of the estimated patient exposure for your marketed products in each EEA country and the total exposure in the EEA for the period 01.01.2015 – 01.06.2019 per year and cumulatively. Patient exposure should be expressed in number of patients and patient-treatment-years per type of product (i.e. separately for 1-, 3- and 6-month products). Please clearly indicate your method of calculation specifying the assumptions made for dose and duration of treatment.

Please use following table:

Product name	Pharmaceutical forms, presentation and strengths	Indication	EEA country	Packages sold (nr)	Estimated patient exposure (number of patients)	Estimated patient exposure (patient treatment years)
			Total EEA:			

Question 2

Each MAH should search its own database for case reports of medication errors for the period 01.01.2015 – 01.06.2019 using search criteria presented below. The search should not be limited only to reaction field (e.g. appropriate SMQ or HLGT); instead, each MAH should according to its technical possibilities search in additional fields such as case narratives, other free text fields, flags, etc. Whenever possible, EudraVigilance case numbers for case reports should be provided and used throughout the response document.

Search criteria:

- SMQ Medication errors (broad)
- SMQ Lack of efficacy (narrow)
- SOC Product issues
- HLT Reproductive hormone analysis

Based on the above, the MAHs are requested to provide the following data:

a) Please provide the total number of serious cases, non-serious cases and cases without adverse events (e.g. incident, near-incident, potential errors, errors without harm, intercepted errors) received per year and cumulatively. Data should be presented per EEA country and in total.

b) Please perform a detailed root cause analysis of medication errors and discuss whether different root causes could be related to specific characteristics of the product or patient care. Reference is made to available guidance in this field. When analysing special attention should be given to cases associated with lack of efficacy and handling errors (e.g. errors during the product preparation and administration). Please also provide information on how and who has identified the medication error and whether the medication error was noted before, during or after administration of the product. Any additional relevant information on root cause analysis should be provided and discussed.

Question 3

Please describe all steps of the product preparation and administration of your product(s). Discuss for each step the potential for medication errors and product issues, their potential consequences (such as reduced efficacy, no efficacy, AEs) and measures that could be implemented to minimise them (such as change of the device, product reformulation).

Question 4

Please present the following information on all of the risk minimization measures (RMMs)/activities that have been implemented to address the issue of medication errors and product issues with leuprorelin-containing products: types of RMMs/activities and dates of implementation in each EEA country (Table 2).

Dates on implementation refer to the date when a certain RMM/activity was actually implemented by a MAH/NCA in a country (e.g. date of distribution of educational material, date of implementation of SmPC update recommended by PRAC, change of the device, product reformulation, etc.). Details of RMMs/activities and their effectiveness in terms of number of reported cases of medication errors/lack of efficacy/product issues/abnormal reproductive hormone analysis should be discussed.

Table 2: Risk minimisation measures/activities per EEA member state

Member State	Type of RMM/activity	Date of implementation

Question 5

Based on the review of available data and taking into account results from root cause analysis, please provide proposals and justifications for RMMs and activities, which may prevent medication errors and product issues. In addition, proposals should be made on how their effectiveness could be monitored taking into account their feasibility.