NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Germany (BfArM):

Product Names in the Referring Member State	Eligard and other leuprorelin-containing products
Active substance(s)	Leuprorelin - depot injections
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holders	Various

Background

Leuprorelin is a Gonadotropin releasing hormone (GnRH) agonist, which when used continuously leads to a decrease of gonadotropin and sex steroid levels. In male patients the continuous use of leuprorelin leads to a decrease of testosterone below the castration threshold. Eligard and most other leuprorelin-containing depot products are indicated for the treatment of advanced hormone-dependent prostate cancer. Other indications of leuprorelin-containing depot-products are endometriosis, symptomatic uterus myomatosus, breast cancer, uterine fibrosis, and precocious puberty. The efficacy of leuprorelin used for treatment of prostate cancer is monitored by evaluation of serum testosterone levels and Prostate-Specific Antigen (PSA). Leuprorelin is considered effective if a testosterone level below 50 ng/dL is reached (Mottet et al. [1]). Efficacy in female indications is confirmed by low blood concentrations of follicle-stimulating hormone (FSH) and estradiol.

Leuprorelin-containing depot products have a 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 (e.g. prolonged release microspheres suspension and Atrigel). Leuprorelin-containing products are injected subcutaneously or intramuscularly.

Risk for Medication Errors and associated Lack of Efficacy

The different formulations require different handling steps during preparation and administration, which carry the risk for medication errors potentially leading to lack of efficacy. Lack of efficacy associated with handling errors is challenging to detect for leuprorelin-de-

pot formulation. The increase of hormone levels (e.g. serum testosterone) after a misapplication is delayed up to several weeks. Therefore, a treating physician might not associate hormone increase with a previous handling error, especially if administration and evaluation of treatment are performed by different healthcare professionals. Breakthrough testosterone levels in patients treated with GnRH agonists have been reported and are an alternative explanation for increased testosterone levels (Morote, J., et al. 2009 [2]). This complicates establishing a causal link between handling errors and lack of efficacy and may increase underreporting.

Issues to be considered

For Eligard, a detailed analysis of medication errors has been performed. In total, 2,271 cases of handling errors have been reported for the period from 1 January 2012 to 31 December 2018. About 90% of the reported cases included information whether the product was administered or not. In 472 cases (20.8%) of the reported cases Eligard has been administered to a patient following the handling error. In the majority of the other cases the handling error was noted before administration of the product and Eligard was not injected to the patient. In 120 cases lack of efficacy associated with handling errors were reported. As stated above significant underreporting has to be assumed.

The most common handling errors reported for Eligard were syringe issues leading to leakage, which are often associated with the grey stopper left behind in the syringe, issues with the safety needle (e.g. breaking of the needle hub and associated leakage) and handling errors associated with the products viscosity. However, most cases reporting handling errors associated with lack of efficacy lacked details on type of handling error.

The high number of handling errors reported for Eligard led to assess this signal in 2014. [redacted] Besides, since 2014 further risk minimisation measures (educational material, DHPC, training with dummy device, modification of the plunger rod) have been implemented to mitigate the risk of handling errors. In 2019, a new safety needle was introduced.

In May 2019, PRAC remained concerned with the high number of medications errors still occurring with Eligard.

An analysis of EudraVigilance performed for all leuprorelin-containing products however shows that the risk of medication errors is not limited to Eligard. In fact, significant numbers of relevant case reports of different leuprorelin-containing depot formulations were retrieved in EudraVigilance. Furthermore, analysis of EudraVigilance revealed that cases coded as product use issues were also indicative for medication errors.

No cases indicative of medication error were retrieved for non-depot formulations of leuprorelin.

Case reports of medication errors and product issues associated with adverse reactions from EudraVigilance for leuprorelin-containing products (01-Jan-2018 until 20-May-2019, EEA only)

	Total	***Eligard***	***Enantone and other products using release microspheres suspension***	***Implants by Sandoz/Hexal***	***Product not reported***

SMQ Medication Errors	341	115	168	33	25
SOC Product Issues	144	72	41	19	1

The medication errors and product issues reported for leuprorelin-containing products included cases with the potential for lack of efficacy (e.g. leakage leading to incomplete product injection reported for Enantone or implants remaining in the device).

However, a detailed analysis of all medication errors associated or not with adverse reactions is currently not available for other leuprorelin-containing products.

Notably, as per EudraVigilance analysis an increase of cases reporting medication errors, product issues and lack of efficacy has been observed for all leuprorelin-containing products since 2018.

When comparing EudraVigilance data of leuprorelin-containing products, the inherent limitations of spontaneous reporting have to be acknowledged. For example, reporting of handling errors of Eligard might have been influenced by the measures already taken for Eligard (e.g. DHPCs in 2014 and 2017), which might have increased awareness for the risk of lack of efficacy due to medication errors. It should also be considered that the differences in product presentations (implant, solution, atrigel) may directly influence the likelihood to detect a medication error. Handling errors reported for Eligard are often associated with product leakage, which is more likely to be noticed during the product administration process than an implant remaining in the device. Taken together, the true extent of handling errors and associated lack of efficacy of the different leuprorelin-containing products is currently unknown.

Overall, the significant number of medication errors, observed for leuprorelin-containing depot products, which may lead to lack of efficacy in affected patients, pose a serious risk to public health. Further action is considered warranted to further characterise and mitigate the risk of handling errors and associated risk of lack of efficacy of leuprorelin-containing depot-injections.

In view of the above and the necessity to take an action at EU level, Germany (BfArM) considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed [redacted] Date June 7th, 2019

References:

[1] Mottet et al: EAU Guidelines: Prostate Cancer: https://uroweb.org/guideline/prostate-cancer/, accessed 07 June 2019

[2] Morote, J., et al. Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. BJU Int, 2009. 103: 332