Annex II

Scientific conclusions

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Leuprorelin-containing depot medicinal products are indicated for prostate cancer, breast cancer and conditions that affect the female reproductive system (e.g. endometriosis, uterine fibroids) and early puberty. They can be injected subcutaneously or intramuscularly and they are available as implants in pre-filled syringe, powder and solvent for injection (solution or suspension) and powder and solvent for injection in pre-filled syringe.

These products differ in the complexity and number of reconstitution and administration steps and carry the risk for medication errors (MEs), leading in some cases to underdosing and consequently a lack of efficacy (LoE).

The process for reconstitution of Eligard (from Astellas) is particularly complex, with the highest number of steps involved and the majority of MEs reported for this product. For this product, over the years, several risk minimisation measures (RMMs) have been implemented to mitigate the risk of MEs potentially leading to LoE including educational materials, Direct Healthcare Professional Communication (DHPCs) in 2014 and 2017, training with dummy device, modification of the plunger rod and the introduction of a new safety needle in 2019. In 2014, the marketing authorisation holder (MAH) Astellas committed to the development of a new device for Eligard to facilitate the reconstitution and administration and therefore to minimise the risk of MEs. In 2018, Astellas reported that the development of this device failed due to major changes in the product composition required for this modification. It was noted that despite all the RMMs implemented, the number of MEs reports remained high. Appropriate regulatory action is, therefore, necessitated in order to reduce the risk of MEs through an improved administration device.

The reports of MEs and cases coded as product issues are not limited to Eligard, but they also concern other leuprorelin-containing depot products as well. No cases indicative of MEs was retrieved for non-depot formulations of leuprorelin.

On 07 June 2019 therefore, Germany triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of the leuprorelin-containing depot medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked and give a scientific opinion on the MEs and the associated lack of efficacy.

The PRAC adopted a recommendation on 14th May 2020 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Although the benefit of leuprorelin-containing medicinal products in their approved indications is established, it is apparent that the efficacy of treatment can be compromised if the patients do not receive the intended dose. A number of MEs leading to underdosing and consequently associated with LoE were noted. The assessment of post-marketing safety data related to MEs indicated that in the majority of cases where information about indication was available, the products involved were used in treatment of prostate cancer. Taking into consideration that prostate cancer is a life-threatening disease, compromised efficacy due to MEs is not acceptable.

Case reports of MEs were assessed for each leuprorelin-containing depot product based on data retrieved from the EudraVigilance (EV) database, submitted by the MAHs and limited data through the literature. Despite the limitations of spontaneous reporting, the data showed that products with more complex or higher number of reconstitution steps in their preparation and administration have more potential for MEs. This is in line the fact that the highest number of MEs reports was obtained for

Eligard, which is also the product with the most complex reconstitution process. The reporting rate for Eligard, was approximately 10 times higher compared to the reporting rate of the dual-prefilled syringe (DPS) formulations from Takeda and affiliated MAHs, which have significantly fewer reconstitution steps for reconstitution (3 reports/1000 patient-years versus 0.35 reports/1000 patient-years, respectively). Concerning the Lutrate Depot, a product with also a level of complexity in its reconstitution process, the reporting rate is 1.80 reports/1000 patient-years. The reporting rate of MEs of the products of the Novartis group corresponds to 0.31/1000 patient-years, while for other implants the reporting rate is null.

The highest reporting rate of MEs with Eligard, could be partially attributed to the increased awareness of the healthcare professionals (HCPs) following twice the DHPC dissemination and the provided educational materials from Astellas. However, one can argue that the same factors may have had an indirect impact also for the other leuprorelin-containing depot products causing an increase in their reporting rates as well.

MAH Astellas has over the years implemented several RMMs to minimise the risk of MEs, nevertheless, MEs are still being reported, indicating that these RMMs are not sufficiently effective. The MAH failed to develop a device with two prefilled syringes and fewer and less complex reconstitution steps that would replace the current device.

Taking into consideration the seriousness of the risks associated with these MEs, the fact that the implemented RMMs have not sufficiently minimised this risk and that other leuprorelin-containing depot medicinal products which have this type of device (dual chambers) have fewer MEs reported, the PRAC considered that the development of a new device is the most effective measure to minimise the risk of MEs associated with Eligard and therefore for reducing the resulting risk of lack of efficacy of this product. Therefore, it should be included as a condition to the respective marketing authorisations and the relevant variations should be submitted to the relevant national competent authorities (NCAs) by 31 October 2021.

In the interim period, routine RMMs in the form of updates to the product information are deemed necessary in order to increase awareness of physicians to minimise the risk of MEs associated with the use of Eligard. These updates include amendments to sections 4.2 and 4.4 of the summary of product characteristics (SmPC) to inform the HCPs for the potential of MEs associated with the use of the product and highlight that the instructions for reconstitution and administration must be strictly followed. When a ME is suspected, the patient should be monitored appropriately.

The majority of the MEs associated with Lutrate Depot (from GP-Pharm and associated MAHs) revealed that they occurred during a specific step of the preparation process. Therefore, the PRAC considered that section 6.6 of the SmPC should be revised to include clearer instructions for reconstitution and the packaging of the product should be modified in order to facilitate the access to instructions for use for HCPs and highlight the importance of reading the instructions before reconstitution and administration. The PRAC concluded that the current RMMs implemented along with the PI amendments proposed, are sufficient to minimise the risk of MEs for this product.

The PRAC noted that essential data needed to perform a detailed root-cause analysis was missing in approximately 45% of the cases retrieved from EV. Therefore, all MAHs are requested to perform a follow-up of each reported case of MEs as per the Good practice guide on recording, coding, reporting and assessment of MEs (EMA/762563/2014). Follow-up of MEs cases should be considered as a routine pharmacovigilance activity through which MAHs should try to obtain relevant information not provided in the initial report.

Based on the review of all available data, the PRAC is of the opinion that 'medication errors resulting in lack of efficacy' should be considered as important identified risk for all leuprorelin-containing depot

products and should be included in existing risk minimisation plans (RMPs). Applicable pharmacovigilance activities and risk minimisation measures should be listed in the RMPs accordingly. Leuprorelin-containing depot products that do not have an RMP in place, do not need to introduce it, but have to include 'medication errors resulting in lack of efficacy' as a safety issue of special concern that needs to be monitored through periodic safety update reports (PSURs). The PSUR submission frequency should be revised from current 5 years to 2 years.

The analysis of reports of MEs showed that different types of HCPs committed errors such as physicians and nurses, but also patients as well. Given the complexity of the reconstitution process of the leuprorelin-containing depot medicinal products and in order to minimise the MEs performed by patients, all MAHs, should ensure that leuprorelin-containing depot medicinal products are handled, prepared and administered only by healthcare professionals who are familiar with these procedures. Hence, a statement that the product should be handled, prepared and administered only by healthcare professionals who are familiar with these procedures should be added in section 4.2 of the SmPC and section 3 of the PL of all leuprorelin-containing depot medicinal products. In this respect, any reference in the PI on self-administration by the patient should be deleted.

Given the higher reporting rate of MEs observed after the previous DHPC dissemination for Eligard, it is considered that the DHPCs have had an impact in raising the awareness of the HCPs on the potential for MEs. Hence, the PRAC agreed on the dissemination of a DHCP to highlight the importance of following strictly and carefully the reconstitution process, for all leuprorelin-containing depot medicinal products.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of leuprorelin-containing depot medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for leuprorelin-containing depot medicinal products.