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Pharmacovigilance Risk Assessment Committee (PRAC)

# Assessment report

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

INN: leuprorelin-containing depot medicinal products

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

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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## List of abbreviations

AE: Adverse Events

DHPC: Direct health care professional communication

DPS: Dual-Chamber Prefilled Syringe

EEA: Economic European Area

EV: EudraVigilance

FSH: Follicle-stimulating hormone

GnRH: Gonadotropin releasing hormone

HCP: Healthcare Professional

HE: Handling Error

LoE: Lack of Efficacy

ME: Medication Error

MS: Member State

PIL: Patient Information Leaflet

PSA: Prostate-Specific Antigen

QR: Quick response

RMMs: Risk Minimisation Measures

SmPC: Summary of the Product Characteristics

SMQ: Standardised MedDRA Query

# 1. Information on the procedure

Leuprorelin is a gonadotropin releasing hormone (GnRH) agonist. Leuprorelin-containing depot products are authorised in the 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, powders and solvents for the preparation of injections and powders and solvents for injections in pre-filled syringes. Leuprorelin-containing depot products are injected subcutaneously or intramuscularly.

The presentations as well as the preparation, reconstitution and administration process vary among the products. There have been numerous reports of medication errors (MEs) leading to lack of efficacy (LoE) associated with leuprorelin-containing depot medicinal products, albeit with different reporting rates per medicinal product. The highest number of MEs have been reported over the years for Eligard (Astellas). Despite several risk minimisation measures (RMMs) that have been implemented for this product, they have not been proven to be sufficiently effective as MEs still occur.

In view of the above, the German national Competent Authority (NCA) BfArM considered that the risk of MEs leading to underdosing and potentially to lack of efficacy (LoE) should be reviewed.

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 LoE.

The scope of this procedure includes all strengths and formulations for the leuprorelin-containing depot medicinal products.

# 2. Scientific discussion

## *2.1. Introduction*

Leuprorelin is a gonadotrophin releasing hormone (GnRH) agonist. GnRH agonists are analogues of natural GnRH and exhibit enhanced potency and a prolonged duration of action compared to natural GnRHs.

The secretion of pituitary gonadotropins (follicle-stimulating hormone [FSH] and luteinising hormone [LH]) requires pulsatile secretion of GnRH from hypothalamic nuclei, allowing the re-expression and up-regulation of GnRH receptors on the pituitary gland at regular intervals between the pulses. In contrast, constant receptor stimulation by GnRH analogues initially causes immediate release of the deposited gonadotropins which starts two to three days after the administration and lasts for about one week. The chronic exposure to GnRH agonists results in the down-regulation of the GnRH signalling pathways suppressing LH and FSH secretion and therefore testosterone production. The decrease in testosterone production is generally reversible upon cessation of GnRH agonist therapy.

Leuprorelin-containing depot medicinal products have a duration of action of 1,3 or 6 months and they are used for a variety of conditions; treatment of advanced hormone-dependent prostate cancer, breast cancer, endometriosis, uterine myoma, uterine fibrosis and precocious 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.

Cases of MEs leading to LoE associated with leuprorelin-containing depot medicinal products have been reported due to complex reconstitution and administration process of some presentations.

The process for reconstitution of Eligard (from MAH Astellas) is particularly complex, with the highest number of steps involved and the majority of medications errors 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, 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 MAH Astellas committed to the development of a new device for Eligard in order 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.

Prior to the initiation of this referral procedure, Germany conducted an EudraVigilance (EV) analysis which showed that the risk of MEs is not limited to Eligard, since relevant case reports of MEs and cases coded as product issues are reported for other leuprorelin-containing depot products as well. Therefore, all leuprorelin-containing depot medicinal products are included in the scope of this procedure. No cases indicative of medication error were retrieved for non-depot formulations of leuprorelin.

In this assessment, the PRAC considered the totality of the data submitted by the marketing authorisation holders (MAHs), the MAHs responses to PRAC list of questions and list of outstanding issues, the EV analysis (with a data lock point on 27 July 2019) performed by EMA and the Rapporteurs, comments received by the MS and data from the literature.

***Description of the assessed products***

Seven companies have provided responses to the list of questions (LoQs) / outstanding issues (LoOIs) requested by PRAC: Amdeepcha, Astellas, Endomedica, GP-Pharm (incl. Angelini Pharma, PharmaS, Mercury, Vianex and Gedeon Richter), Takeda (including Orion and AbbVie), Teva (incl. affiliated companies). The Novartis group (Hexal / Sandoz) did not provide response on the LoQs but provided responses to the subsequent LoOIs. A brief description of the assessed products is presented below. However, products from several other MAHs have been included in this procedure.

Amdeepcha: Leuprorelin Acetate 11.25mg is an implant in pre-filled syringe for subcutaneous use. It is indicated for endometriosis and uterine fibroids and it is authorised in the UK.

Astellas: Eligard is marketed in three presentations of 7.5 mg (monthly product), 22.5 mg (3-monthly product) and 45 mg (6-monthly product), for the treatment of advanced prostate cancer. It is authorised in 28 EEA MS.

Endomedica: Leugon 11,25 mg is an implant in a pre-filled syringe. The implant is ready-to-use and no preparation is required prior to the administration. It is indicated for the symptomatic treatment of hormone dependent advanced prostate cancer and it is only marketed in Germany since October 2018.

GP-Pharm (and associated companies): Lutrate Depot 1-month (3.75 mg) and Lutrate Depot 3-month (22.5 mg) for intramuscular injection are authorised for the treatment of advanced prostate cancer. A common response from all affiliated MAHs was provided.

Takeda (and affiliated companies Abbvie and Orion): Takeda is the originator of leuprorelin acetate containing products. Takeda products include Enatone, Sixantone, Terantone, Prostap and others. They are available in 1-month (3.75 mg) and 3-month (11.25 mg) sustained-release injections indicated for

several conditions including treatment of prostate cancer, breast cancer, endometriosis, uterine fibroids, central precocious puberty and preservation of ovarian function. Authorised routes of administration are subcutaneous and intramuscular (varies by country and indication). There is also a 6-month (30 mg) sustained-release formulation authorised only in the treatment of prostate cancer and is administered only subcutaneously. A common response from all affiliated MAHs was provided.

Takeda also markets the 1- and 3-months vial and ampoule presentation and a 3-months dual-chamber prefilled syringe (DPS) presentation (Elitryan). In the majority of the MS, leuprorelin depot products by Takeda (3.75 mg 1-month, 11.25 mg 3- months, and 30 mg 6- months, where authorised) are now presented in a DPS containing a powder and vehicle for suspension, although the vial and ampoule presentation is still available in a few MS. The 6-months dosage form has been presented in the DPS since its initial authorisation in 2007.

Teva: Leuprorelin-ratiopharm 11,25 mg is an implant in pre-filled syringe for 3-monthly administration authorised for the treatment of advanced prostate cancer. Teva's product, which was marketed in Germany in February 2019, is a ready for injection product.

Novartis Group (Sandoz, Hexal): The Novartis products include 1- and 3-months implants in pre-filled syringe for subcutaneous use.

## 2.2. Data on efficacy

This procedure is related to MEs potentially associated with LoE which are due to errors in the reconstitution and administration processes of the assessed products. There are no elements reviewed within this procedure which question the efficacy of leuprorelin and the assessed products in their authorised indications, when they are used and handled correctly.

***Prostate cancer***

Prostate cancer is the second most commonly diagnosed cancer in men accounting for 15% of all cancers diagnosed. The European Association of Urology (EAU), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines recommend androgen deprivation therapy (ADT) using either medical or surgical orchiectomy as the initial hormonal therapy for men with advanced prostate cancer.

Leuprorelin-containing depot products are used as an alternative to surgical castration in metastatic prostate cancer and locally advanced prostate cancer. They are also used as adjuvant hormone therapy after radiotherapy and after radical prostatectomy in patients with locally advanced prostate cancer at a high risk of disease progression. Compared to orchiectomy, medical castration with GnRH agonists offers the potential to reverse hypogonadal symptoms upon cessation of therapy and avoid the psychological issues associated with surgical castration.

The efficacy of leuprorelin used for the treatment of prostate cancer is monitored by evaluation of serum testosterone levels and prostate-specific antigen (PSA) as defined by castration levels used for the currently authorised products at < 50 ng/dL (1.7 nmol/L). The efficacy in clinical trials has been shown to be between 94.0% (3-month leuprorelin product marketed by Teva, Endomedica, Amdeepcha[1]) and 99% (Eligard 22.5 mg[2]), 96.6% for 3-month implants by Sandoz/Hexal[3], 96.8%

[1] Public Assessment Report Leuprolin-ratiopharm 11,25 mg Fertigspritze mit Implantat; https://mri.cts-mrp.eu/Human/Downloads/DE_H_4781_001_PAR.pdf
[2] SmPC Eligard 22.5 mg
[3] Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. Tunn UW, Wiedey K. Prostate Cancer Prostatic Dis. 2009;12(1):83-7. doi: 10.1038/pcan.2008.52. Epub 2008 Nov 25.

Lutrate 3.75 mg[4], 96% Trenantone[5], 94% Sixantone[5] and 98% Eligard 7.5 mg[6]. The small differences in efficacy are possible and are attributed to the different trial design, different drug release system and the amount of active substance in the products.

Overall, there are several studies assessing the efficacy and the tolerability of leuprorelin depot products which concluded that the products are well tolerated and can reliably lower serum PSA and testosterone levels [7] [8] [9] [10]

***Other indications***

Leuprorelin-containing depot preparations are also used as an adjuvant therapy of hormone receptor positive breast cancer and in metastatic hormone receptor positive breast cancer in pre and perimenpausal women in addition to tamoxifen and with aromatase inhibitors, Fulvestrant and CDK 4/6 inhibitors. Aromatase inhibitors are contraindicated in women with premenopausal endocrine status without adequate ovarian suppression; therefore the American Society of Clinical Oncology Guideline (ASCO) recommends the use of GnRH agonists. The European Society of Medical Oncology (ESMO) advises to apply depot products on a monthly basis to optimize ovarian suppression[11].

As per ESMO guidelines for breast cancer in young women, Leuprorelin-containing depot preparations should be used as part of care to premenopausal women on chemotherapy for fertility preservation as GnRH agonists preserve ovarian function in women receiving chemotherapy, reducing the risk of early menopause and increasing the chances for future fertility. GnRH agonists are also used for suppression of the hypothalamic-pituitary-gonadal axis which is prematurely activated in gonadotropin-dependent precocious puberty. Reactivation of hypothalamic-pituitary-gonadal axis and onset of puberty after cessation of the treatment is rapid and no long-term side effects are expected[12].

Endometriosis is characterised by oestrogen dependent growth of the endometrial glands and stroma outside the endometrial cavity. GnRH agonists decrease oestrogen levels by blocking ovarian oestrogen production and hence regression of endometriotic implants[13]. Uterine myoma are benign neoplasms of uterus composed of muscle cells. Complex biochemical interactions are involved in the regulation of myoma growth and ovarian steroid hormones have significant influence on this process thus hypoestrogenism induced by GnRH agonists leads to the tumour reduction[14].

[4] SmPC Lutrate 3.75 mg
[5] Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. Tunn UW, Wiedey K. Prostate Cancer Prostatic Dis. 2009;12(1):83-7. doi: 10.1038/pcan.2008.52. Epub 2008 Nov 25.
[6] SmPC Eligard 7.5 mg
[7] Ulf, W. T., 2011. A 6-month depot formulation of leuprolide acetate is safe and effective in daily clinical practice: a non-interventional prospective study in 1273 patients. BMC Urol, Volume 11, p. 15.
[8] Braeckman, J. & Michielsen, D., 2014. Efficacy and tolerability of 1- and 3-month leuprorelin acetate depot formulations (Eligard®/Depo-Eligard®) for advanced prostate cancer in daily practice: a Belgian prospective non-interventional study. Arch Med Sci, Volume 10(3), pp. 477-483.
[9] Ohlmann, C. H. & Gross-Langenhoff, M., 2018. Efficacy and Tolerability of Leuprorelin Acetate (Eligard®) in Daily Practice in Germany: Pooled Data from 2 Prospective, Non-Interventional Studies with 3- or 6-Month Depot Formulations in Patients with Advanced Prostate Cancer. Urol Int, Volume 100(1), pp. 66-71.
[10] Ouzaid, I. & Rouprêt, M., 2011. The role of a 6-month depot form of hormone therapy in the treatment of advanced hormone-dependent prostate cancer: Results from the 'ELIRE' observational study. Prog Urol, Volume 21(12), pp. 866-74.
[11] Paluch-Shimon, S. et al., 2017. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast, Volume 35, pp. 203-217.
[12] Brito, V. N., Latronico, A. C., Arnhold, I. J. & Mendonça, B. B., 2008. Update on the etiology, diagnosis and therapeutic management of sexual precocity. Arq Bras Endocrinol Metabol. 2008 Feb; 52(1):18-31., Volume 52(1), pp. 18-31.
[13] Rafique, S. & DeCherney, A. H., 2017. Medical management of endometriosis. Clin Obstet Gynecol, Volume 60(3), pp. 485-496.
[14] Rackow, B. W. & Arici, A., 2006. Options for medical treatment of myomas. Obstet Gynecol Clin North Am, Volume 33(1), pp. 97-113.

## *2.3. Data on safety*

### 2.3.1. Literature

Several studies assessing the efficacy and the tolerability of leuprorelin-containing depot formulations have shown that the products are well tolerated and can reliably lower serum PSA and testosterone levels [15] [16] [17] [18]. However, no publications specifically describing MEs with leuprorelin depot preparations have been reported in the literature.

### 2.3.2. EudraVigilance (EV) analysis

Following the PRAC request, the EMA performed an EV analysis of the medication errors for leuprorelin-containing depot medicinal products.

The search criteria included all cases that have any of the following MedDRA preferred terms: Lack of efficacy/effect Standardised MedDRA Query (SMQ) (narrow), Product Issues SOC, Medication error SMQ (broad) and reproductive hormone analyses HLT, from start of recording to 27 July 2019.

In the EV analysis, a total of 1,707 reports were identified, with medication error counting for 865 cases, LoE for 759 cases, product issues for 252 cases and reproductive hormone analyses HLT for 195 cases. The most frequently events reported as serious were LoE with 82.9% (629/759 cases) and reproductive hormone analyses with 80.5% (157/195 cases).

The most frequent preferred term for the Lack of effect SMQ was drug ineffective with 614 reports, out of which 521 cases were reported as serious. The most reported medication error SMQ terms were inappropriate schedule of product administration (100), intercepted medication error (88) and wrong technique in product usage process (88). The majority of cases reporting inappropriate schedule of product administration (82/100) were serious while the majority of cases reporting the other two PTs were non-serious.

Sixty-four reports have terms for both medication error and lack of effect combined. This constitutes 7% of all cases of MEs and 8% of all cases of lack of effect. In 104 case reports, the blood testosterone increased, with 80% of these being classified as serious. Furthermore, 101/195 cases reporting terms of reproductive hormone analysis also report terms for at least one of the remaining concerns of interest.

Of the 1,707 reports of concerns of interest 911 were in EEA, 487 in USA, 115 in Canada, 51 in Japan, and 143 in all other countries. The EU/EEA country with the highest count of reports is Germany followed by France, Netherlands and Italy.

When stratified by year, it is obvious that the concerns of interest have increased significantly over the period of 2018 to July 2019. Two peaks in 2014 and 2017 in the reporting rate have been identified, the reason of which is unclear. It can be assumed that it could be due to a genuine raise of MEs or it could be due to increased awareness following the regulatory actions taken, such as the DHPCs, in 2014 and 2017 and other risk minimisation measures that could have influenced the reporting.

[15] Ulf, W. T., 2011. A 6-month depot formulation of leuprolide acetate is safe and effective in daily clinical practice: a non-interventional prospective study in 1273 patients. BMC Urol, Volume 11, p. 15.
[16] Braeckman, J. & Michielsen, D., 2014. Efficacy and tolerability of 1- and 3-month leuprorelin acetate depot formulations (Eligard®/Depo-Eligard®) for advanced prostate cancer in daily practice: a Belgian prospective non-interventional study. Arch Med Sci, Volume 10(3), pp. 477-483.
[17] Ohlmann, C. H. & Gross-Langenhoff, M., 2018. Efficacy and Tolerability of Leuprorelin Acetate (Eligard®) in Daily Practice in Germany: Pooled Data from 2 Prospective, Non-Interventional Studies with 3- or 6-Month Depot Formulations in Patients with Advanced Prostate Cancer. Urol Int, Volume 100(1), pp. 66-71.
[18] Ouzaid, I. & Rouprêt, M., 2011. The role of a 6-month depot form of hormone therapy in the treatment of advanced hormone-dependent prostate cancer: Results from the 'ELIRE' observational study. Prog Urol, Volume 21(12), pp. 866-74.

Most reports of the concerns of interest were made in the US. The EEA country with the highest count of reports is Germany followed by France and Netherlands.

In addition to the EV analysis performed by EMA, the Rapporteurs performed also a separate EV analysis using the same search criteria, applying the same DLP and for the same period. The analysis had similar results to the one performed by EMA, however it has also identified some additional elements.

In most of the reported cases, the indication for leuprorelin use was unknown, however in cases where the indication was reported, the most commonly reported was prostate cancer (128/347). For the other indications such as breast cancer, endometriosis or precocious puberty accounted only few cases were identified. Most of the patients (75%) were male.

In 44 out of the 50 of the serious cases, disease progression was reported. When ADR was reported, the most commonly reported reactions were terms related to therapeutic ineffectiveness (24) (PT drug ineffective), administration site reactions (14) (PT injection site pain), reproductive hormone analyses (32) (PT prostatic specific antigen increased, PT blood testosterone increased and PT blood testosterone abnormal).

There were 104 out of the 347 reports of general MEs without further specification. A total of 118 cases of MEs reported were associated with syringe issues. 52 reports were related to problem during product reconstitution and 52 report considered errors and issues with needle. In 11 cases wrong route of administration was reported and 10 cases were related to storage issues where product either was not stored or administered at the correct temperature. In most of the cases, the medication was administered by either nurse (170/347), physician (31/347) or unspecified healthcare professional (3/347).

There is a number of cases where patients were self-administering the medication (38/347). When reports of patient errors where analysed by a medicinal product name it was noted that most of the errors were concerning Enantone (30/38) but it is not specified at which step of product preparation or administration error occurred. When further analysis was performed by the MAH, the reports were qualified by probable medication error during process of product preparation/administration.

Analysed data confirmed that products which have more steps in product preparation and administration, such as Eligard, have more potential for medication errors. Eligard was involved for almost half of the reported cases (169/347) and Takeda products were involved in 123 cases. The Sandoz/Hexal products followed with 46 cases, while there were 9 cases without the product involved to be identified.

For Eligard, most commonly errors (32/169) were described at step where the two syringes are mixed. Error either occurred due to inappropriate attachment of two syringes where product leak happened or inadequate number of back and forth movements between two syringes which lead to product viscosity issues. Errors where short (blue) plunger was inadequately removed from syringe B were reported in 31 cases. This led either to product leak or to difficulty in product reconstitution since back and forth movement between two syringes were hard to perform. Third most common step where errors were reported is safety needle attachment. Overtightening of needle to syringe was reported to lead to needle cracking and product leak. In some cases, too loose attachment of needle led to product leak at junction between safety needle and syringe. Other steps where errors were recorded was step where product is applied to the patient in 11 cases where wrong route or wrong injection technique was used. In 9 cases product was inadequately stored or was not at proper temperature for administration which led to product viscosity issues. A summary of the steps of the product preparation that the error occurred is presented in the **table 1** below.

**Table 1: Steps of product preparation where error occurred for Eligard**

| Step where error occured | No. of cases |
|---|---|
| mixing two syringes | 32 |
| short plunger removal | 31 |
| needle attachment | 24 |
| application of product | 11 |
| storage | 9 |
| unspecified | 62 |
| **Total** | **169** |

### 2.3.3. Overview of medication errors per MAH

The MAHs performed a search in their own databases for the period 01 January 2015 to 01 June 2019 applying the same search criteria as described in section 2.3.2. A summary of the results of each MAH's analysis is presented below in addition to an overview of the preparation steps of each leuprorelin product as well as an analysis on the risk of MEs in each step. Based on this analysis in combination with the reporting rate of each product, the RMMs (routine or additional) already in place are discussed.

***Exposure***

The exposure varies among different leuprorelin-containing depot products and among different indications. As shown in **table 2**, for the period from January 2015 to June 2019 in the EEA, the highest exposure corresponds to products marketed by Takeda, followed by Astellas (Eligard) and GP-Pharm. The product of the MAH Amdeepcha (Leuprorelin Acetate 11.25mg implant) has been authorised only in 2019 in one MS (UK), therefore no sales and exposure data were available at the time of the assessment. Leugon 11,25 mg implant from Endomedica is only authorised in two EU countries (Germany and Luxemburg) since October 2018 and only 23 packages have been sold according to the MAH.

When looking at the exposure, it should be taken into consideration that Takeda products are indicated for more than one indication including endometriosis, uterine myoma, female breast cancer, prostate cancer, central precocious puberty (CPP) and female infertility.

**Table 2. Comparative Total Patient exposure in the EEA for the period 01.01.2015 – 01.06-2019**

| MAH | Number of Patient-years |
|---|---|
| **Amdeepcha** | **-** |
| **Astellas** | **567,33** |
| **Endomedica** | **5** |
| **GP Pharm** | **17,99** |
| **Takeda** | **1,043,58** |
| **Teva** | **1,147** |

#### *2.3.3.1. Amdeepcha, Endomedica and Teva*

The leuprorelin products from Amdeepcha, Endomedica and Teva have been present only in few MS of the EU market and for a short duration of time. No cases of MEs, LoE, product issues or abnormal reproductive hormone analysis have been reported with these products.

The products are ready to use implants in pre-filled syringes indicated for prostate cancer. No reconstitution steps are required prior to application. The required steps to administer these products are summarised below:

Disinfect the injected area / Check whether the implant is in the intended position in the application device / Remove the safety ring-clip / Remove the protector needle cap / Introduce the needle into the tissue at a slight angle

Amdeepcha identified as the main risk associated with their products to be infections due to loss of sterility and abscess formation that may decrease absorption and lead to a decreased efficacy. The possible consequence of decreased absorption due to abscesses formation is stated in the product's SmPC and PL. Lack of efficacy due to device failure or drug administration error is also identified as an important potential risk in the product's RMP. Clinical measure to monitor the product's efficacy is recommended in section 4.8 of the SmPC with a recommendation to measure serum concentrations of testosterone 28 days after each injection and before each re-administration.

Other administration errors may occur during the injection itself, resulting in incorrect implantation of the leuprorelin implant or failure to inject the implant. To address this risk, the MAH Amdeepcha provides administration training trough a video to the HCPs, although this is not part of the RMMs. In addition, the MAH foresees an annual review of all cases of suspected device failure and drug administration error which allows to continuous monitor the MEs spotted during clinical practice.

The MAH Endomedica stated that there is no potential for MEs or product issues, if all steps of the administration are followed as per the instructions provided in the SmPC and PIL. According to the MAH, the instructions on use which are given on the inner side of the carton box and that following these instructions are clear and explicit.

Similarly, Teva's product is a ready to use injection with no need for reconstitution. The few steps required prior to administration have been described and the potential for medication error has been discussed in each of them by the MAH. The step with the higher risk is identified to the removal of the safety ring, where any unintended pressure on the plunger could pull the fixed implant stick into the needle which can lead to the loss of the implant. Such potential medication error can be avoided if the needle shows upwards during the removal of the protective cap. To address the identified risks, despite no report of medication error has been received, Teva has implemented routine RMMs including instruction for use and training to HCPs with the product launch. Additionally, application demonstrations using a placebo device is given by sales representatives to HCPs.

#### *2.3.3.2. Takeda/Abbvie/Orion*

Takeda and affiliated companies are the MAHs for several leuprorelin products including single dose for injection in a dual-chamber prefilled syringe (DPS) and vial/ampoule formulations for subcutaneous and intramuscular use. The DPS formulation contains the powder in one chamber and the solvent in the other chamber. As presented in previous section, the products of Takeda and affiliated companies have the highest exposure, with more than 1 million patient-years, among all leuprorelin-containing depot products. The highest exposure is attributed to the fact that the products are indicated for various conditions apart from prostate cancer.

A total of 1,020 cases of MEs were identified by the MAHs (Takeda and affiliated companies). Of these, 92% of the cases were considered non-serious and 72% of the MEs were reported without an associated adverse reaction. The most common PT was drug ineffective (182), followed by intercepted medication error (166) and medication error (113).

When narrowing down the search for cases indicated potential problems with the preparation or administration of the product plus and the SMQ product issues, a total of 398 unique cases of MEs have been identified.

A total of 36 cases under product administration error PT were reported. These include 10 events of injection of the vehicle alone without the leuprorelin powder, 9 cases of delayed administration due to prescription issues or administrative error, 4 cases of inadequate reconstitution (the powder was not completely dissolved or the residual powder remained in syringe), and 13 cases of incomplete drug administration or other administration errors like omitting to let out air before administering injection and not changing the needle after product reconstitution. It is noted that events like injection of vehicle without leuprorelin and not changing the needle after reconstitution solely apply to the vial/ampoule presentation which is currently available in only 3 MS (France, the Netherlands and Poland).

There were 8 cases reporting PT product reconstitution quality issue. Difficulties in reconstituting the product resulted in an accidental loss of the product and product leakage. There were 15 cases with PT syringe issues, most of them involved syringe functioning issues (plunger blocked, increased pressure in syringe, unable to push down piston) and liquid spillage. Other reported cases include missing vehicle in the leuprorelin box in which case the water was used as vehicle, incomplete mixing, and prescribed dose being pulled out from the prefilled syringe to a dosage syringe. The MAH attributed these events to an improper use of the syringe.

Among the 398 handling errors reports, there were 7 LoE identified reports associated with different handling errors such as incorrect temperature storage, incorrect preparation (the drug power was not dissolved or the syringe was not been shaken until the suspension appears milky), wrong technique in product administration by the HCP and difficulties in product reconstitution.

It is noted that most of the MEs associated with LoE are related to the reconstitution and administration process of the drug.

As mentioned above, Takeda and affiliated companies have different depot leuprorelin formulations authorised and a proper evaluation on the distribution of errors by pharmaceutical form could not be performed, since details per pharmaceutical form were not available in the reports. Therefore, the MAH analysed the number of reports in countries and years where only DPS formulations were available and in countries where there was an overlap of DPS and vial/ampoule presentations, but only estimations can be done due to the number of assumptions made.

**Table 3** shows that the highest values of reporting rates of MEs were found in countries where DPS formulations overlap with vial/ampoule formulation (ranging from 0.89 to 1.23 HEs events per 1000 patient-years exposure), whereas in countries with only DPS formulations the overall reporting rate of MEs varies from 0.00 to 0.31 events per 1000 patient-years. The overall reporting rate of MEs of the Takeda products is estimated to be 0.35-0.41 reports/1000 patient-years.

**Table 3, MEs based on different pharmaceutical forms and reporting rate per year**

| Year | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Formulation | No. of HE | Reporting Rate | No. of HE | Reporting Rate | No. of HE | Reporting Rate | No. of HE | Reporting Rate | No. of HE | Reporting Rate | No. of HE | Reporting Rate |
| DPS with SD | 22 | 0.12 | 31 | 0.17 | 65 | 0.36 | 100 | 0.53 | 34 | 0.43 | 252 | 0.31 |
| DPS without SD | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Overlap of DPS with SD and DPS without SD | 1 | 0.05 | 7 | 0.33 | 1 | 0.05 | 9 | 0.42 | 6 | 0.69 | 24 | 0.24 |
| Overlap of DPS with SD and vial/ampoule | 18 | 0.42 | 40 | 0.93 | 48 | 1.17 | 41 | 1.05 | 14 | 0.87 | 161 | 0.89 |
| Overlap of DPS without SD and vial/ampoule | 5 | 0.96 | 4 | 0.79 | 10 | 2.29 | 7 | 1.45 | 0 | 0.00 | 26 | 1.23 |
| **Overall Total** | **46** | **0.18** | **82** | **0.32** | **124** | **0.49** | **157** | **0.60** | **54** | **0.50** | **463** | **0.41** |

DPS: dual-chamber prefilled syringe; HE: handling error; SD: safety device.
The patient exposure details used for reporting rate calculation are based on the response to Article 31 of Directive 2001/83/EC, Procedure Number: EMEA/H/A-31/1486 dated 09 September 2019 (see Appendix 1).

Due to differences among the formulations, the MAH provided 3 separate tables with preparation steps with the potential for MEs, consequences, and measures to minimize issues **(Tables 4,5,6)**

The DPS marketed by AbbVie is identical to the Takeda/Orion DPS but does not include the safety device.

**Table 4. Leuprorelin DPS presentations steps with potential for medication errors and mitigation measures (Takeda and Orion products)**

**Table 3.p Leuprorelin DPS Preparation Steps With Potential For Medication Errors and Mitigation Measures (Takeda and Orion Products)**

| Preparation Step | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|
| Screw the plunger rod into the end stopper until the stopper begins to turn.<br>The needle is free and covered by a normal cap. Do not touch the device around the needle. [a]<br>Break up any lumps in the powder by gently tapping the syringe. [b] | Potential to pull the plunger rod after screwing in to place. | Possible leakage backwards. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| Holding the syringe upright, release the diluents by slowly pushing the plunger until the middle stopper is at the blue line in the middle of the barrel.<br>NOTE: Pushing the plunger rod quickly or over the blue line will cause leakage of the suspension from the needle. | Syringe not held upright during release of vehicle. | Potential leakage from needle. If significant loss of product occurs and product is administered to patient could result in underdose with consequent impacts on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| | Pushing the plunger rod too quickly or over the blue line | Leakage from needle and/or at the reverse end of the syringe. If significant loss of product occurs and product is administered to patient could result in underdose with consequent impact on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| Gently tap the syringe on the palm keeping the syringe upright to thoroughly mix the particles to form a uniform suspension. The suspension will appear milky.<br>NOTE: Avoid hard tapping to prevent the generation of bubbles. | Inability to thoroughly mix the suspension | Potential to block the needle. If it is still possible to administer product to patient it could result in underdose with consequent impact on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |

**Table 3.p Leuprorelin DPS Preparation Steps With Potential For Medication Errors and Mitigation Measures (Takeda and Orion Products)**

| Preparation Step | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|
| Remove the needle cap and advance the plunger to expel the air from the syringe. | Syringe not held upright during release of air. | Potential leakage from needle. If significant loss of product occurs and product is administered to patient could result in underdose with consequent impact on efficacy | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| The product should be mixed and used immediately. | Suspension settles out very quickly if not used immediately after reconstitution. | If not used immediately and then administered to patient, potential for incomplete administration of dose resulting in underdose with consequent impact on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| At the time of injection, check the direction of the safety device (with round mark face up). Inject the entire contents of the syringe subcutaneously or intramuscularly as you would for a normal injection | Failure to check direction of safety device renders administration difficult due to impedance by safety device.<br><br>Failure to administer the entire syringe contents | Potential for incomplete administration of dose resulting in underdose with consequent impact on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |
| Withdraw the needle from the patient. Immediately activate the safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt. | Not implemented or inadequate activation of safety device | Possibility of needlestick injury | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |

DPS: dual-chamber prefilled syringe.
[a] Additional instruction specific to Italy.
[b] Additional instruction specific to France.

**Table 5. Leuprorelin DPS presentations steps with potential for medication errors and mitigation measures (Abbvie products)**

**Table 3.q Leuprorelin DPS Preparation Steps With Potential For Medication Errors and Mitigation Measures (AbbVie Products)**

| Preparation Step | | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|---|
| 1 | To prepare for an injection, screw the white plunger to the bottom of the injection syringe until the rear rubber stopper starts to rotate (Picture 1).<br>  <br>Picture 1 | Potential to start pushing the plunger and releasing vehicle with syringe not in upright position. | Possible leakage from needle if vehicle introduced in to front chamber. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |
| | | Needle cap could be removed if rotated in anticlockwise direction. | Loss of sterility representing hazard for patient.<br>Potential for needlestick injury to operator. | |
| | | If overtightened cap may not be able to be removed. | Product cannot be administered. | |
| 2 | Hold the syringe upright, with the tip of the injection needle facing upwards. Push the plunger in SLOWLY until the front part of the rubber stopper in the middle reaches the blue line in the middle of the syringe, which should take about 6-8 seconds (Picture 2). | Syringe not held upright during release of vehicle. | Potential leakage from needle. If significant loss of product occurs and product is administered to patient could result in underdose with consequent impacts on efficacy | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |
| | | Pushing the plunger rod quickly or over the blue line. | Leakage from needle. If significant loss of product occurs and product is administered to patient could result in underdose with consequent impacts on efficacy | |

**Table 3.q Leuprorelin DPS Preparation Steps With Potential For Medication Errors and Mitigation Measures (AbbVie Products)**

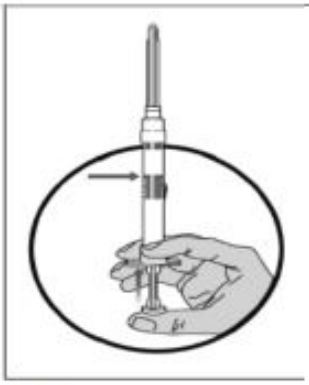
| Preparation Step | | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|---|
| |  Picture 2 | | | |
| 3 | Gently tap the syringe against the palm of your hand as shown (Picture 3) to thoroughly mix the particles of medicine with the diluent. The suspension will appear milky. If particles remain stuck to the stopper, then tap the syringe with your finger.  Picture 3 | Inability to thoroughly mix the suspension | Potential to block the needle. If product is still able to be administered to patient could result in underdose with consequent impacts on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |
| | | Over-vigorous tapping or shaking will cause bubbles/foaming to occur | Difficult to remove bubbles/foam prior to injection. Suspension could settle whilst awaiting dissipation of bubbles. | |
| 4 | Remove the needle guard by pulling it directly upwards (do not twist) and push the plunger in to remove all the air from the syringe | Inability to remove needle cap | Product cannot be administered | Product information adequately describes the preparation step |

**Table 3.q Leuprorelin DPS Preparation Steps With Potential For Medication Errors and Mitigation Measures (AbbVie Products)**

| | Preparation Step | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|---|
| | (Picture 4).<br>  <br>Picture 4 | | | and potential issues that may occur if not done correctly |
| 5 | Clean the injection site and inject the entire liquid subcutaneously (under the skin) or intramuscularly. Change the injection site regularly (Picture 5).<br>  <br>Picture 5 | Suspension settles out if not used immediately after reconstitution | If administered to patient potential for incomplete administration of dose resulting in underdose with consequent impacts on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly |

**Table 6. Leuprorelin vial and ampoule: preparation steps with potential for medication errors and mitigation measures**

Table 3.r Leuprorelin Vial and Ampoule: Preparation Steps With Potential For Medication Errors and Mitigation Measures

| Preparation Step | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|
| Place your thumb on the blue point and break the ampoule of solvent by flexion at this point. | | | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| Withdraw contents of ampoule of solvent using a syringe and introduce into the vial of powder for reconstitution of the suspension. This solvent is specific for Enantone LP 3.75 mg: it should never be replaced by another solvent. | Use of a different vehicle | Powder cannot be adequately mixed and possibility of underdosing or inability to administer. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| Shake the preparation well. | Inadequate mixing | Potential to clog needle. Inability to administer dose. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |
| Aspirate the mixture obtained; make sure that the whole of the suspension has been drawn. | Failure to draw up the whole suspension. | Possibility of underdose potentially leading to lack of efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |

Table 3.r Leuprorelin Vial and Ampoule: Preparation Steps With Potential For Medication Errors and Mitigation Measures

| Preparation Step | Potential for medication error and product issues | Potential consequences | Measures to minimize issues |
|---|---|---|---|
| Inject the suspension immediately after reconstitution using a syringe for subcutaneous or intramuscular route. | Suspension settles out rapidly. | If not used immediately and then administered to patient, potential for incomplete administration of dose resulting in underdose with consequent impact on efficacy. | Product information adequately describes the preparation step and potential issues that may occur if not done correctly. |

For the DPS presentations, it is observed that possible leakage can occur on several steps in preparation due to several reasons including syringe not held upright during release of vehicle, pushing the plunger rod too quickly or over the blue line, syringe not held upright during release of air, not immediate use of the product after reconstitution (the suspension settles out very quickly) and inability to thoroughly mix the suspension.

For the vial and ampoule presentations, as potential ME has been identified the use of a different vehicle, inadequate mixing, failure to draw up the whole suspension and rapidly settling out of suspension.

For all these potential MEs there is a potential for incomplete dose administration and potentially LoE. This analysis is line with the 7 MEs associated with LoE as described in the previous paragraph.

The MAH concludes that the most appropriate measure to minimise the potential risk of MEs is the clear and accurate description of the preparation steps in the PIL and the MAH argues that the instructions in the PIL of the leuprorelin DPS formulation provide sufficient details to avoid MEs if followed correctly.

The routine RMMs in place by the MAH to address and minimise the above mentioned identified potential risks are summarised below:

- The legal (prescription) status of the product: prescription-only medication for specialist use. The product should be administered under the supervision of a medical professional experienced in the diagnosis and treatment of the approved indications.

- Pack design: The risk of error by administering the wrong duration/strength has been minimized by colour differentiation of the trade names and strengths.

- SmPC and PIL: The SmPC (Section 4.2 and 6.6) and PIL (Section 6) with detailed instructions for preparation and administration, including pictures illustrations.

In some MS, additional steps have been taken to prevent MEs by training and educating practitioners.

- A separate Health Professional's User Leaflet, containing detailed instructions for the preparation and administration by the HCP, in addition to the package leaflet in the UK and in IE.

- A quick response (QR) code to the SmPC linking to a video demonstration of preparation of the DPS in Italy.

- Additional education materials with detailed instructions and video on the preparation / handling of the product in Italy and France.

***Takeda products used for self-administration by patients***

When discussing the RMMs in place, the MAH mentioned the prescription status of the product (prepared and handled only by HCPs) as a routine RMM to eliminate the risk of MEs. The PRAC noted that all leuprorelin-containing medicinal depot products are not authorised or intended for self-administration by patients in EEA countries with the exception of Enantone in France and Italy, where a total of 255 cases of MEs related to Enantone were identified. A further evaluation of the available data per country has been conducted in relation to the number of MEs attributable to patients and HCPs.

**Table 7: MEs attributed to HCPs and patients in Italy and France for Takeda products**

| Country of Incidence | HCPs | Patients | Total |
|---|---|---|---|
| France | 106 | 10 | 116 |
| Italy | 60 | 79 | 139 |
| **Total** | **166** | **89** | **255** |

HCP: healthcare professional; HE: handling error.

**Table 7** shows that in Italy more MEs are attributed to patients than HCPs (79 vs 60). The MAH's position that only 26 self-administration associated HEs are identified in Italy was noted by the PRAC, however it is unclear why such a high number of MEs is attributed to patients if it is not related to self-administration. This analysis was taken into consideration in combination with the EV analysis presented in section 2.3.2, in which it was identified that the one third of the MEs reports for Enantone are caused by patients. Also, when reports of patient errors from all MAHs were analysed together, it was seen that in approximately 79% of the cases, the product involved was Enantone.

The MAH provided information that for the DPS 1M, 3M, and 6-month depot presentations in France, self-administration is mentioned in the SmPC. Patients who are comfortable with and capable of self-administration may be permitted by their prescriber to self-administer the product after instructions by a trained healthcare provider. In contrast, the MAH has stated that the Italian PI does not contain specific recommendations regarding self-administration by patient, rather that instructions are intended for a general user.

#### *2.3.3.3. Astellas*

A total of 2,833 cases have been retrieved by the MAH, the majority of them (95%) classified as non-serious. In most cases (2,361) no adverse events were reported, however in the rest of the cases, no details about adverse events were provided. The highest number of cases was reported under the term SMQ Medication errors, following SOC Product issues and SMQ Lack of Efficacy.

**Table 8. Overview of search strategies and number cases by seriousness**

| Search Strategy | Total Cases | Non-serious | Serious |
|---|---|---|---|
| SMQ Medication errors (broad) | 1,752 | 1,696 (97%) | 56 (3%) |
| SMQ Lack of efficacy (narrow) | 242* | 187 (77%) | 55 (23%) |
| SOC Product issues | 786* | 775 (99%) | 11 (1%) |
| HLT Reproductive hormone analysis | 53* | 35 (66%) | 18 (34%) |
| **Total** | **2,833 (100%)** | **2,693 (95%)** | **140 (5%)** |

SMQ: Standardized MedDRA Query; SOC: System Organ Class; HLT: High level term.

* These numbers represent all cases retrieved with the search strategy; including those that are not due to a medication error.

A total of 1,591 reports of handling errors were retrieved (each case describes one or more handling errors) during the reference period. Handling errors were defined as errors or issues in storage, preparation, reconstitution, and/or administration of the product. An overview of all categories of handling errors is presented in the table below.

**Table 9. Eligard handling errors categories**

| Handling Error Category | Description |
|---|---|
| 1. Storage issue | Cases that reported storage of the product not in accordance with the labelled instructions. |
| 2. Product not brought to room temperature before reconstitution | Cases that describe that the product was not brought to room temperature prior to reconstitution, including cases in which the product was too viscous (item #9). |
| 3. Grey stopper left behind | Cases that describe incorrect removal of the blue plunger rod that is attached to a grey cap (stopper) from the syringe containing the powder, resulting in retention of the grey stopper, an inability to reconstitute, and often syringe leakage. |
| 4. Syringe issue with leakage | Cases that describe an issue with the syringe and product leakage (regardless of root cause), including<br>• Cases describing leakage after retention of the grey stopper (item #3) and<br>• Cases that do not specify the site of the syringe leakage, nor the timing of the leakage.<br>Note: Cases that specifically describe the syringe leakage as having occurred at the site of attachment between the needle and the syringe and cases that do not specify the site of the syringe leakage but describe it as having occurred after the attachment of the needle or during injection are not categorized as "syringe issue with leakage," but are instead categorized separately as "needle/hub issues" (item #7). |
| 5. Syringe issue with no leakage | Cases that describe a problem with the syringe, with no indication of product leakage. |
| 6. Mixing issue | Cases that describe insufficient mixing (i.e., < 30 round trips), or shaking rather than transferring the material between the 2 syringes. |
| 7. Needle/hub issue | Cases that suggest an issue with the attachment between the needle and the syringe hub, whether or not associated with leakage, including:<br>• Cases in which the needle was overtightened when attaching it;<br>• Cases describing syringe leakage at the site of attachment between the needle and the syringe;<br>• Cases that do not specify the site of the syringe leakage but describe it as having occurred after the attachment of the needle or during injection. |
| 8. Other needle issue | Cases that describe an issue with the needle other than overtightening (e.g., breakage or faulty needle) without indication of an issue with the syringe. |
| 9. Product too viscous | Cases that specifically mention that the product was too viscous before or after correct mixing, which may or may not be reported in combination with other HE categories (e.g., failure to bring the product to room temperature [item #2]). |
| 10. Solvent issue | Cases that describe an issue related to the solvent such as lack of solvent or use of an alternative solvent. |
| 11. Administered powder or solvent only | Cases that describe administration or attempted administration of only the solvent or powder. |
| 12. Unspecified handling/ reconstitution error | Cases that describe a HE (or suspected HE) but provide insufficient information to allow further categorization. |
| 13. Incomplete dose/ portion of drug remained in syringe | Cases that describe administration of an incomplete or partial dose because the product reportedly remained in the syringe. |

In the **Table 10**, a summary of all handling error rate per category is presented. The most frequently reported ME categories were syringe issue with leakage (1.1 per 1000 patient/years, grey stopper left behind (0.7 per 1000 patient/years) and needle/hub issue (0.7 cases per 1000 patient/years).

**Table 10: Summary of medication errors for Eligard for the period January 2015 – June 2019 in EEA**

| Medication Errors | Number |
|---|---|
| Syringe issue with leakage | 599 |
| Grey stopper left behind | 396 |
| Needle/hub Issue | 388 |
| Product too viscous | 150 |
| Unspecified | 150 |
| Mixing issue | 120 |
| Syringe issue without leakage | 95 |
| Product not at room temperature | 79 |
| Storage issue | 47 |
| Solvent issues | 47 |
| Other needle issue | 38 |
| Solvent/powder only | 20 |
| Incomplete Dose/Portion left in syringe | 17 |
| **TOTAL** | **2,146** |

The MAH pointed out that syringe leakage while attempting to mix the contents of the 2 syringes (60 times in total) is a common result when the grey stopper is not properly removed. If the secondary grey stopper is not removed (as advised by the SmPC) there may be greater pressure upon mixing. This pressure leads to a higher potential for the product to leak once the syringes are disconnected. Therefore, it is noted that syringe issue with leakage and grey stopper left behind errors are often reported together.

Information relating to the HCP who was responsible for the ME was available only in 15% cases. Where information was available, the error was attributed to the nurse, physician and other healthcare professional in 63%, 22% and 13% of the cases respectively.

In 20% of the identified cases reported that Eligard was administered to the patient despite the occurrence of the medication error (0.6 per 1000 patient/years).

In 3.6% (0.1 per 1000 patient/years) of all identified cases of MEs reported LoE (unconfirmed and confirmed). 1.2% of them had confirmed LoE (i.e., reported testosterone levels > 50 ng/dL and/or 1.735 nmol/L measured ≥ 2 weeks after the reported Eligard administration during which the HE was reported to have occurred).

The types of MEs led to the LoE were not specified, although, as described below, there are several steps in the product preparation where an error can result in incomplete administration. While number of cases where MEs resulted in LoE was generally low (58), the total number of LoE cases in the MAH's database was significantly higher (242). Lack of efficacy reports without MEs were not further analysed by the MAH and it is possible that an error had not been recognised by the reporter.

Considering the overall data on MEs covering complete years, the MEs decreased in number, although in 2018, the number of reports were still over 2/3 of the number of errors reported in 2015, despite all measures put in place over these years. In absolute numbers, 432 reports related to MEs were registered in 2018, and 312 reports have been reported in the first 5 months of 2019. Overall, reporting rate is higher in the Q1 2019 than in Q1 2015. Even the errors classified as grey stopper left behind reaches in Q1 2019 almost similar levels of Q1 2015, despite changes in the device.

Eligard is provided in a kit with 2 trays and 2 syringes and has a complex reconstitution process with 15 steps. The MAH provided a detailed analysis of each preparation step along with a discussion on the potential for MEs, their potential consequences and measures that has been implemented to minimise them.

For steps 1, 3, 4, 14 and 15, the MAH did not identify a potential for ME and their potential consequences and routine measures to minimise the risk include information given in SmPC section 6.6.

For steps 5, 6, 7, 9, 10 and 13 the potential ME concerns syringe issue with leakage and/or incomplete dose and portion of drug remaining in the syringe with potential consequence of incomplete administration of the intended dose. Measures to minimise risk include information given in SmPC section 6.6.

For step 2 in which the blue coloured short plunger rod should be pulled out but without unscrewing, together with attached grey stopper from Syringe B and discarded (it should not be attempted to mix the product with two stopper in place), the MAH states that possible ME includes incorrect removal of the blue plunger rod that is attached to a grey stopper from the syringe containing the powder with the potential consequences of inability to reconstitute and often syringe leakage. Measure to minimise this risk included modification of the device so that it is easier to correctly remove the blue plunger rod and the grey stopper together. This variation has been approved in 2015.

For step 8 in which the product should be thoroughly mixed by gently pushing the contents of both syringes back and forth between syringes (60 times in total), the potential ME concerns mixing issue with potential consequence of product leakage. This can occur as the user may partially unscrew the syringes as well as product being too viscous with potential consequence that the product will be too viscous and difficult to administer. Measures to minimise risk include information in section 6.6 of the SmPC, as well as the development of a dual chamber single syringe device with fewer and easier handling steps. However, the MAH stated this development has been proven unfeasible from a technical point of view, since it would result to significant quality modifications of the product.

For step 11 in which the Syringe B should be held upright and the white plunger held back to prevent loss of the product and then the safety is needle secured to Syringe, the potential ME concerns a needle/hub issue and syringe issue with leakage, with potential consequence of overtightening of the needle which may result in cracking of the needle hub resulting in leakage of the product during injection. Several measures have already been implemented to minimise this risk such as update of the information in section 6.6 of the SmPC, DHPC dissemination in 2017, which reinforces the handling instructions with the safety needle, the replacement of Magellan by new Terumo safety needle (variation approved on January 2019), updated educational materials (video, website and poster) with testosterone monitoring in all patients and handling instructions for the new Terumo safety needle and QR code leading to instructional video.

For step 12 in which the safety shield should be moved away from the needle and protective needle cover should be pulled off prior to administration, the potential ME concerns an issue with the needle other than overtightening (e.g. breakage or faulty needle) or an issue with the syringe with potential consequence of inability to administer the Eligard injection. Measures implemented to minimise the risk

include information given in SmPC section 6.6. as well as distribution of DHPC that reinforces the handling instructions with the new safety needle.

The reconstitution process of Eligard encompasses 15 steps, including a transfer of the product from both syringes back and forth 60 times in total, during approximately 60 seconds. The most common potential ME identified is syringe issue with leakage, which can occur at almost every step of the preparation with incomplete administration of the intended dose potential consequence is and subsequently cause lack of therapeutic response.

To address the risks discussed above, Astellas has to date implemented several routine and additional RMMs which are summarised below:

- SmPC updates to reinforce the attention of the HCP on the correct preparation and administration of the product. Examples of the SmPC wording is presented below:

  Information given in SmPC section 6.6: "If the product is not prepared using the proper technique, it should not be administered, as LoE may occur due to incorrect reconstitution of the product."

  Instruction for HCPs to watch the instructional video before reconstitution. The video can be found under www.eligard.eu. This proposed with variation currently in clock stop.

- Dissemination of DHPC (in 2014 and 2017) and educational material that reinforces the need for adherence to the product label instructions for the appropriate storage, reconstitution and administration of Eligard to inform the HCPs about the potential consequence of LoE if the instructions are not followed correctly. The second dissemination of DHPC addressed handling errors was related to overtightening of needle.

- Development and implementation of a multi-modal educational program involving dissemination of various tools such as posters, instructional video, website, and smartphone application with the aim to reinforce the importance of appropriate storage, preparation, reconstitution and administration of Eligard.

- Testosterone monitoring: Approval of new testosterone monitoring requirements in France and documentation of testosterone level on prescription.

- Device modifications: Initially the device was modified in such way that it was more difficult to remove the blue plunger rod without removing the grey stopper in 2015. In January 2019, a second device modification took place concerning the introduction of the new safety needle (Terumo) aiming to reduce the risk of overtightening and prevent needle hub cracking. The implementation of the new safety needle into the market has been started in May 2019, therefore the effectiveness of this measure has not been assessed in this referral.

In addition to the above RMMs, the MAH, following the PRAC recommendation of November 2014 and after an update of the RMP, committed to the development of a dual chamber single syringe device. The new device would be developed to achieve fewer and easier handling steps and was tested on the approved Eligard formulation. According to the MAH this formulation failed the extended release specifications (controlled release rate) at 12 months as an interaction between leuprorelin acetate and its solvent caused the drug substance to be physically unstable. The MAH claimed that any improvement of the formulation would lead to substantial changes to the qualitative and quantitative characteristics of Eligard, with no guarantee of success. Eventually, the MAH considered this plan is not feasible and abandoned the development failing to fulfil its commitment for a simpler device development.

#### *2.3.3.4. GP-Pharm (and associated companies)*

GP-Pharm and associated companies (Angelini, Vianex, Gedeon etc.) are the MAHs for Lutrate 1-month and 3-month depot formulations, which are intended for intramuscular injection and are indicated for prostate cancer. The MA of these products is held, in different countries of the EU, by different MAHs, which provided a common response and are represented by GP-Pharm.

The MAH has described the 22 steps involved in preparation and administration of Lutrate depot along with a risk analysis based on the principles described in the Failure Mode and Effects Analysis (FMEA) guidance [19]. The risk is classified depending on the Risk Profile Number (RPN) score as follows: low risk with RPN from 1 to 20, medium risk with RPN from 21 to 40, and high risk with RPN from 41 to 100.

As a general comment, the preparation steps are counted in a different way by every MAH; therefore, the number of steps needed for reconstitution are not directly comparable. For example, the 22 steps described by GP Pharma are not directly comparable with the 15 steps described for Eligard, as they compromise some instructions common for all injectable products regardless of the substance, the MAH or the device (for example: wash your hands, select the correct strength, place the tray in a clean surface etc.).

Based on the RPN scores obtained, the risk of MEs associated to Lutrate Depot is considered low since all steps have RPN score lower to 21 and two steps have scores of 20. The 2 steps carrying RPN score of 20 are still in low risk category but at the upper limit. These 2 steps include step 13 in which the vial should be gently swirled for approximately one minute until a uniform milky-white suspension is obtained and step 21 in which the product should be intramuscularly injected into the gluteal area. There were also 2 steps which carry the RPN score 15: step 14 for which it is noted that a quick handling is essential since in order to avoid separation of the suspension, they should be proceeded to the next steps without delay and step 16 in which plunger rod should be pulled back slowly to draw the reconstituted Lutrate Depot into the syringe.

There is the potential risk not to mix the suspension correctly leading to the separation of suspension and underdosing. It is noted that a special characteristic of Lutrate depot is that the vial contains the powder and the prefilled syringe the diluent. In case of not transferring the whole amount of the suspension back into the syringe, could potentially lead to underdosing.

A total of 33 cases of MEs have been recorded in the period 1 January 2015 to 1 June 2019 for the Lutrate depot products. The highest number of reports without adverse events concerned intercepted errors occurring at different steps of product preparation.

In 2 cases, occupational exposure and incorrect drug administration duration was reported. In 1 case, LoE was related to the error in product reconstitution and administration. In 1 case the product was administered subcutaneously instead of intramuscularly. The administration lasted 40 minutes and the patient experienced stinging. It can be assumed that this was done intentionally (off-label use) as other leuprorelin depot products indicated for endometriosis are administered subcutaneously. One case where the product was administered every 15 days for 3 months instead of three-monthly was also presented.

When the cases were analysed based on the step of the reconstitution process occurred, it was shown that 86.5% of the cases occurred in early stages of the reconstitution and administration process and lead to errors that prevent the product to be administered to the patient. 78.4% of the errors were related to an issue with the insertion of the transfer device into the vial stopper which lead to breakage

[19] QI Essentials Toolkit: Failure Modes and Effects Analysis (FMEA). Institute for Healthcare Improvement, 2017

/ deformation of the device spike needed to perforate the vial stopper and made impossible to continue with the reconstitution process.

A more detailed analysis by the MAH has revealed that most medication errors associated to Lutrate Depot reconstitution and administration process are related to the insertion of the transfer device into the vial without complete or no removal of flip-off cap which accounts for 16% of the total handling errors received, and insertion of the transfer device without centering it in the vial stopper and inserting it in a perpendicular direction to the vial, fact that leads to transfer device spike deformation, accounting for the 62% of the total handling errors received.

The overall reporting rate of MEs of the Lutrate has been estimated to be 1.8 / 1000 patient years.

The MAH has implemented several measures to address the risk of potential MEs and product issues.

- Training sessions with video showing the detailed process for correct product preparation and administration (at the time of product launching/introduction in a new health care setting).

- Use of demo kits in order to have active and practical demonstration of product reconstitution and administration (at the time of product launching/introduction in a new health care setting).

- Dissemination of educational materials including a brochure with detailed step-by-step explanation of correct reconstitution and administration process (at the time of product launching/introduction in a new health care setting).

- Direct mobile phone line in order to immediately respond to possible issues that might arise.

- Reminder training sessions upon request or *in situ* when a notification of a medication error is received; In those cases, the MAH contacts the person that made the handling error, the step of the process of administration/reconstitution that was incorrectly handled is detected and company personnel performs a training session in situ, emphasizing the four points previously specified.

#### *2.3.3.5. Novartis group (Hexal/Sandoz)*

The MAH did not submit a response to PRAC LoQs and so the MEs occurred with these products were only analysed and discussed based on data collected in the EudraVigilance analysis and data submitted by the MS as comments during the assessment.

The Hexal and Sandoz products under the scope of this referral include 1- and 3-months implants in pre-filled syringe for subcutaneous use. Despite the products are ready to use, they require some attention during the administration process. The needle has first to be completely inserted and then pulled back approximately 1cm to create a puncture canal for the implant. The implant is injected in the puncture canal. If the needle is not drawn back before injection there is a risk that the implant might remain in the needle.

A total of 80 cases were identified using the SMQ medication error and 36 cases using the SOC Product issues. The majority on the medication error cases were related to the administration process or the device, e.g. product administration error (n=13), wrong technique in product usage process (n=10), syringe issue (n=7), wrong technique in device usage process (n=7).

Of the 80 cases, 8 reported LoE. Six (6) cases were associated with the administration of the product: device malfunction (n=4), complication of device insertion (n=1), and product administration error (n=1). The MAH stated that a causality for LoE could not be ruled out with respect to medication error reported. Two cases reported increased testosterone indicating an insufficient leuprorelin dose for testosterone suppression. For the other cases no information on kind of LoE was provided.

According to the data provided, the reporting rate of HEs corresponds to 0.31/1000 patient-years. Overall, the MEs reported indicate that some users have issues with the administration of the product, although the number of reported events is low.

# 3. Discussion

***Eligard***

Data retrieved by the EV analysis and by the MAH Astellas reveal that the highest number of MEs reports were associated with Eligard. The reporting rate of MEs for Eligard was estimated to be 3 /1000 patient-years.

The process for reconstitution and administration of Eligard is the most complex one with many steps involved in the procedure. The product is provided in a kit in 2 trays and 2 syringes, and the process encompasses 15 steps, including a transfer of the product from both syringes back and forth 60 times in total, during approximately 60 seconds. The most frequently reported handling error was syringe issue with leakage, which can occur at almost every step of the reconstitution process. Product leakage can lead to incomplete administration of the intended dose and consequently lack of therapeutic effect.

As presented previously, since 2014 Astellas has implemented a number of RMMs including DHPC dissemination (twice), PIL updates, educational materials and device modifications concerning the blue plunger rod removal and the introduction of a new safety needle. The impact of the modification of the safety needle is still unknown since it was introduced only recently, however the PRAC noted that the rest of the measures had limited effectiveness as MEs are still being reported. Considering the overall data on MEs reported for Eligard for the reference period, although the MEs decreased in number, in 2018 the number of reports was still over 2/3 of the number of errors reported in 2015, despite all measures put in place over these years.

The most important measure to minimise the majority of MEs was to develop a dual chamber single syringe device, but MAH deemed that its development is not feasible. In 2018, the MAH Astellas notified the regulatory authorities, that the development plan of a simpler device, resulting from the 2014 signal procedure, was no longer feasible and that the development program was suspended due to the instability of the product. The MAH failed to fulfil its commitment.

The PRAC noted the presence on the market of depot leuprorelin products in dual-chamber prefilled syringe (DPS) containing the powder in one chamber and the solvent in the other chamber. This indicates the feasibility of manufacturing a leuprorelin product with only one syringe containing both powder and solvent. The analysis of the data suggests that DPS products have fewer and simpler reconstitution steps and are associated with less MEs, despite the greater exposure.

Overall, taking into consideration the seriousness of the risks attached to these medication errors, the fact that the implemented RMMs have not sufficiently minimised this risk, and that other leuprorelin-containing depot products which have this type of dual device 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 that this measure is key for reducing the risk of lack of expected efficacy of this product.

Therefore, MAH Astellas is requested to develop an administration device for Eligard with simpler and fewer reconstitution steps, for example by having the two syringes pre-connected, allowing the product to be ready for mixing. The objective of this proposed device variation must be the simplification of the reconstitution process while addressing the MEs that could potentially lead to LoE in the treatment of patients with advanced prostate cancer.

The MAH has proposed, as part of this referral procedure, a development plan for a device modification that will reduce the complexity of the reconstitution process, decreasing the numbers of preparatory steps from 14 to 9 steps. The projected final device variation consists of two syringes that are pre-connected and their content is ready to be mixed.

According to the proposed modification, the handling steps from 2 up to (and including step) 6, as presented in the SmPC section 6.6, will be removed. The Syringe B will no longer require the removal of the secondary grey stopper and will not require the insertion of the white plunger rod. The Syringe A will not require opening of the tip cap and the two syringes will not be required to be connected manually by the HCP. The preparatory steps removed are considered by the MAH the most laborious ones, which have a higher chance of resulting in MEs and potential under-dosing if not carried out properly. The MAH has identified and discussed the main technical challenges envisaged in this device modification which include the sterilisation of the device with the pre-inserted white plunger rod and the development of a connector which must guarantee no leakages during storage and during the reconstitution steps.

In addition, MAH Astellas has presented a second proposal, referred to it as back-up plan, should the first proposal for device modification fails. The MAH stated that this proposal would be worked on, in parallel with the development plan A. The proposed back-up plan of Syringe B variation concerns the removal of the short blue plunger rod attached to the secondary grey stopper and the pre-insertion of the white plunger rod in Syringe B during the manufacturing process. In practice, this variation will lead to Syringe B being ready to couple to Syringe A, reducing the reconstruction process by two steps.

The PRAC noted that the most frequently reported ME categories for Eligard, were 'syringe issue with leakage', 'grey stopper left behind' and 'needle/hub issue'. The first proposed device modification for a DPS reduces the reconstitution steps by 5 and has the potential to address MEs issue such as with leakage and grey stopper left behind. On the other hand, the back-up plan will reduce the reconstitution process by two preparation steps, but only one step among these two has the potential for error, targeting the risk of the ME 'grey stopper left behind'. Measures to minimise this risk were taken again by the MAH in 2015 with a device modification aiming to increase the difficulty to remove the blue plunger rod without removing the grey stopper. However, the effectiveness of this modification was limited, taken into consideration that the reporting rate of the ME 'grey stopper left behind' is similar before (in 2015) and 4 years after this device modification (in 2019). Based on this observation, the PRAC questions the effectiveness of the back-up plan as proposed by the MAH, and hence it is not endorsed.

The MAH must therefore develop a device encompassing fewer reconstitution steps and with lower risk of medication error. This request is key for the benefit-risk balance of Eligard and is included as a condition to the marketing authorisation of Eligard.

The MAH has provided the forecasted timelines along with milestones for the development plan. The variation is expected to be submitted to the relevant regulatory authorities for assessment by 31 October 2021. An important milestone is set for October 2020, which will provide sufficient confidence whether the connector is effective and ensures segregation of the components. Taking into account the urgency to minimise the risk of medication errors and the technical changes required, the proposed development and timelines are considered appropriate and are endorsed by the Committee.

In the interim period, further measures to minimise the risk of MEs associated with the use of Eligard are considered essential by PRAC. These measures include amendments in sections 4.2 and 4.4 of the SmPC to inform the HCPs for the potential of HEs associated with the use of the product, highlight that

the instructions for reconstitution and administration must be strictly followed and that when a HE is suspected, the patient should be monitored appropriately.

***GP-Pharm and associated companies***

The overall reporting rate of MEs of the Lutrate Depot and associated (GP-Pharm and associated MAHs) has been estimated to be 1.8 / 1000 patient years, corresponding with the second highest reporting rate, following this of Eligard. The complexity of the reconstitution process of Lutrate Depot, where the leuprorelin powder is provided in a vial and solvent in a syringe and need to be reconstituted with a transfer device, is noted.

The PRAC noted that most of the errors occur during the preparation process related to the insertion of the transfer device into the vial and considered that measures focusing in mitigation of this issue would reduce ME rate. The MAH has presented the current PIL in which some unclarities have been identified concerning the instructions of this step. The emphasis of the importance of centering the device and inserting it in a perpendicular direction to the vial is missing, which has been identified as an action to reduce the occurrence of the error by the MAH.

Furthermore, it was noted that the instructions for use are currently included as a tear-off part of the PIL in the commercial package. This fact can lead to some HCPs to not carefully read the instructions for use before proceeding with product reconstitution and administration.

Therefore, the PRAC considered that section 6.6 of the SmPC should be revised to include clearer instructions for reconstitution. Furthermore, the packaging of the product should be modified in order to facilitate the access to instructions for use for the HCPs instead of having them as a tear-off part of the PL and highlight the importance of reading the instructions before reconstitution and administration.

***Takeda and affiliated companies***

The products of Takeda and affiliated companies have the highest exposure, with more than 1 million patient-years, among all leuprorelin-containing depot products. Takeda has products in a vial/ampoule and in dual prefilled syringe (DPS). It was noted that the majority of the reported MEs were associated with product issues and product reconstitution issues. Of note, most of the MEs associated with LoE were related to the reconstitution and administration process of the drug.

The PRAC took into consideration the overall reporting rate of MEs (0.35-0.41 reports/1000 patient-years) and the high exposure of the Takeda products and considered that the current risk minimisation measures are considered sufficient to mitigate the risk of MEs and product issues.

Analysis of reports of MEs from EV database showed that different type of HCPs committed the errors such as physicians and nurses, but also patients as well. The Committee noted that all leuprorelin-containing medicinal depot products are not authorised or intended for self-administration by patients in EEA countries with the exception of Enantone (Takeda) in France and Italy.

The EV analysis presented in section 2.3.2, showed that 79% of all cases of patient errors for leuprorelin were associated with Enantone use, while in Italy more HEs are attributed to the patients than HCPs. Moreover, one third of the MEs reports for Enantone in Italy are caused by patients.

From the description of the reconstruction steps and the MAH analysis, it is obvious that handling, preparation and administration of Enatone is a multiple step process with a potential for MEs. The

PRAC considered that by ensuring that only trained HCPs handle, prepare and administer these products, MEs performed by patients would be eliminated.

Whilst Takeda agrees with removing any reference on self-administration from the French SmPC, they do not agree to remove from the Italian one. The MAH argued that self-administration is a well-established practice in Italy, since the first MA approval of Enantone in 1989, as demonstrated by the existing QR (quick response) code linking to a video which shows preparation and administration performed by a general user without a white coat, in order to avoid the patient identifying him/her with an HCP. The PRAC did not endorse these arguments. The QR code only improves the access to the instructions for reconstitution, thus it should not be perceived as a general agreement of self-administration by patients.

Furthermore, the MAH claimed that mandatory administration by HCPs would place an extra and unsustainable burden on patients and the National Healthcare System as it would generate an increase of clinic visits per year causing disadvantages for the patient's quality of life and adherence to therapy as well as for the sustainability of the Italian National Healthcare System. It was argued that the majority of the patients treated with Enantone are already a particularly vulnerable population due to age, comorbidity and compromised health status therefore it is important to keep these patients outside of the hospital environment, as they are more susceptible to infections. The MAH considered that the ability to self-administer Enantone is essential to maintain continuity of treatment for these severe conditions. Removal of the ability of these patients to treat themselves would result in loss of efficacy and disease progression.

In addition, the MAH mentioned that literature on self-administration of medication after adequate training by HCPs suggests a positive impact on medication adherence and safety, however the relevant reference has not been submitted, therefore no further evaluation of this argumentation could be made.

The PRAC noted the EAU (European Association of Urology) Guidelines for prostate cancer and the AIOM (Associazione Italiana di Oncologia Medica), ESMO (European Society of Medical Oncology), American Cancer Society (ACS), and American Society of Clinical Oncology (ASCO) guidelines for breast cancer which recommend scheduling the follow-up visits for prostate cancer patients at 3, 6, and 12 months after treatment then every 6 months until 3 years and then annually; while patients with breast cancer should be followed every 3 to 6 months for 3 years, then every 6 to 12 months for the next 2 years and then annually.

The PRAC does not agree with the MAH that the administration by HCPs would increase burden on the health care system, since as per the above-mentioned guidelines, regular visits should be performed at a period of 3 or 6 months. The PRAC acknowledged that the oncological patients are particularly vulnerable population and for this they require more specialised monitoring and medical attention, rather than being kept away from hospital visits as it was argued by the MAH. Furthermore, the MAH's rational as to why the administration by HCPs would be an increased burden only for the Italian health care system and not for the other MS, and why only the Italian patients are considered more susceptible to infections is not clear, not substantiated by data and not endorsed by the PRAC.

A different management of the treatment is not justified on the basis of peculiar differences in the Italian National Healthcare System, compared to other EU Healthcare Systems, nor in consideration of the higher risk of COVID-19 infection in hospital settings, since such risk does not differ from that of other EU Countries, and it is expected to be temporary. Also, travel restrictions currently in place in Italy due to COVID-19 is not a valid justification, since travelling for health reasons is permitted.

Overall, the PRAC considers that in order to minimise the MEs by patients, it should be ensured that leuprorelin-containing depot medicinal products are handled, prepared and administered only by HCPs

who are familiar with these procedures, hence any reference on self-administration by patients should be deleted from the SmPC/PIL of Enantone along with the addition of a statement that the product should be prepared and administered only by HCPs.

***Implants***

The implants are 'ready-to use' products in pre-filled syringes with no reconstitution steps. Whilst taking into consideration the limitations of the spontaneous reporting system, the PRAC noted the very low reporting rate of MEs associated with these products (from 0 for Amdeepcha, Endomedica and Teva products to 0.31/1000 patient-years for Novartis group products). The PRAC agreed that the 'ready-to-use' implants in pre-filled syringe with no need of reconstitution process carry a lower potential of MEs compared to products with lengthier and more complex reconstitution process. However, the PRAC took into consideration that these products are available in the market only for a short period of time and their exposure is much lower than other products, hence the lack of reports can be partly due to this reason and should be interpreted with caution. Therefore, the PRAC considered that the routine risk minimisation measures recommended for all products which are discussed in the below paragraph, should also be implemented for implants as well.

***All leuprorelin-containing depot medicinal products***

The PRAC noted that essential data needed to perform a detailed root-cause analysis (for example to identify the preparation and reconstitution steps where error occurred) were missing in approximately 45% of the cases retrieved from EudraVigilance. Therefore, all MAHs are requested to perform a follow-up of each reported case of MEs. When a report of medication error is received, all MAHs should perform an appropriate follow-up, regardless of whether the error was associated with adverse reaction by following recommendations provided in 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 Committee 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 PSURs. The PSUR submission frequency should be revised from current 5 years to 2 years.

The analysis of reports of MEs showed that different type of HCPs committed the 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 HCPs' 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.

## *3.1. Discussion on other risk minimisation measures considered*

The analysis of the submitted data revealed that all stages of the reconstitution and administration process could cause or contribute to the error. Different reasons for the occurrence of this error have been reported. However, the complexity of the reconstitution process was a recurring feature and not limited to one product. Taking into account the outcome analysis and the views of the Member States, the PRAC discussed how the risk minimisation measures already in place could be further strengthened and if further measures should be implemented.

***Testosterone monitoring***

During this procedure, introduction of frequent testosterone monitoring was discussed as a potential RMM. It has been argued that testosterone testing with increased frequency (i.e. 28 days after the administration and prior to each next administration) could enhance the ability for the physician to detect any lack of effect and allow timely intervention (for example re-administer the product).

The efficacy of leuprorelin used for the treatment of prostate cancer is monitored by evaluation of serum testosterone levels and PSA. The castration level used for the efficacy evaluation of the currently authorised products is < 50 ng/dL (1.7 nmol/L). According to the European Association of Urology (EAU) for prostate cancer, testosterone monitoring should be considered as a part of clinical practice for men on GnRH therapy. A 3 to 6-month testosterone level assessment is suggested to ensure castration is achieved and maintained. The PRAC noted that a more frequent or specific timing is not defined.

The MAH Astellas has also proposed the introduction of a more frequent and routine testosterone testing in Eligard's SmPC for all patients in order to further mitigate the risk of lack of efficacy (LoE) due to MEs.

The PRAC also noted that some SmPCs of leuprorelin-containing medicinal products included in this referral already recommend a more intensive monitoring of testosterone levels. For example, the SmPC of the Amdeepcha's product which is an implant, contains the following recommendation: *"The response to Leuprorelin therapy should be monitored by measuring serum concentrations of testosterone 28 days after each injection carried out and before each re-administration of Leuprorelin Amdeepcha and additionally on the basis of other laboratory tests like acid phosphatase and PSA. Abscesses at the injection site occur rarely. In one report of an abscess at the injection site, the absorption of leuprorelin from the depot appeared to be decreased. It is therefore advised to determine testosterone levels in such cases."*

The PRAC noted that the higher frequency of testosterone monitoring is not in line with the recommendations of the Guidelines of the European Association of Urology. It was highlighted that the frequency of testosterone testing should be motivated solely by medical and clinical reasons and not based on limitations of specific products or formulations, as this recommendation is envisaged to ascertain the product's effectiveness as per clinical practice and not to detect any potential medication

error. In addition, testosterone surges above castrate levels during long-term LHRH therapy may be due to a variety of reasons not linked to handling errors.

The PRAC furthermore considered that the more intensive testosterone monitoring would not prevent the medication error, as it does not address the root causes of the problem, but it might just allow earlier observation of a LoE that could result from the medication error. Furthermore, the PRAC considered that more frequent testing would not be proportionate in view of the extra burden for both patients and the healthcare systems. This may lead to decreased patient adherence that would be detrimental.

In view of all the above considerations, the PRAC considered that this is not an appropriate RMM to address the risk of MEs assessed in this referral procedure.

***QR code***

The use of a quick response (QR) code into PI, leading to a video with detailed instructions for product preparation and administration in order to ease access and increase availability of instructions for preparation and administration to HCPs has been discussed.

MAH Astellas has proposed to include a QR code in the SmPC, PIL and poster which allows smartphones to have direct access to the online instructional video. With the QR code, the MAH intends to strengthen the Eligard Risk Management Program with particular emphasis on mitigating MEs by increased awareness and usage of the instructional video. In addition, it is noted that the QR code has already been implemented by some MAHs and in some MS (e.g. Takeda in Italy), however there is not a harmonised approach among the MAHs and for the same MAH across all the MS.

Although, the Committee could recognise some potential of the additional QR code to increase awareness on the preparation and the reconstitution process, it was noted that in order to have a meaningful impact, the QR code should lead to information additional to those already included in the PIs, otherwise a video would be just another means of expressing the same information.

The overall added value of the QR code on the package to reduce the risk of MEs was questioned since the MEs are attributed to the complexity of the product preparation rather than accessibility to the instructions. Furthermore, it was considered that it is unlikely that the HCP would watch the video before preparation and administration if clear instructions are already available in the SmPC and PL of the products.

Therefore, the PRAC considered that the QR code as proposed would not further minimise the risk of medication errors. Instead, the PRAC considered that it would be more valuable to improve the current instructions for products preparation and administration.

***Follow-up questionnaires***

It was noted that data needed to perform a detailed root-cause analysis of MEs, for example to identify the preparation and reconstitution steps where error occurred, were missing in approximately 45% of reported cases and data regarding indication for leuprorelin use and relevant medical history, including patient age, were missing in approximately 60% of cases. Based on this observation the Committee agreed that efforts by all the MAHs should be performed in order to gain more information on the steps causing handling errors and to follow-up on LoE after a medication error occurred.

For Eligard, follow-up questionnaires of reported handling errors are implemented to in order to collect further information on the step that caused the handling error and its consequences, and to obtain more information on LoE cases (e.g. testosterone values).

The PRAC has discussed the implementation of targeted follow-up questionnaires for all leuprorelin-containing depot products, however it was considered that the follow-up data collection as per the provisions of the Good practice guide on recording, coding, reporting and assessment of MEs (EMA/762563/2014) is sufficient to collect comprehensive information for medication error reports contributing to the scientific evaluation of the case.

# 4. Overall benefit/risk balance assessment and recommendations

Although the benefit of leuprorelin-containing depot 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 was 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 EV, 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 handling errors 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 syring (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 it is 0.

The highest reporting rate of MEs with Eligard, could be partially attributed to the increased awareness of the 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 dual device 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. This measure is key for the benefit-risk for reducing the risk of lack of expected efficacy of this product and should be included as a condition to the respective marketing

authorisations and the relevant variation should be submitted to the relevant national competent authorities by 31 October 2021.

In the interim period, routine risk minimisation measures in the form of updates to the product information are deemed necessary in order to minimise the risk(s) of handling errors associated with the use of Eligard. These updates include amendments to sections 4.2 and 4.4 of the 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 (GP-Pharm and associated MAHs) revealed that they occurred during a specific step of the preparation process. Therefore, the PRAC considers 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 Committee 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.

# 5. Risk management

The Committee, having considered all information and data submitted in the procedure, recommends a series of pharmacovigilance activities and risk minimisation measures to minimise the risk of medication errors associated with leuprorelin-containing depot medicinal products.

Medication errors resulting in LoE 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 measures should be listed in the RMPs accordingly.

## *5.1. Pharmacovigilance activities*

### 5.1.1. PSUR monitoring (including change to PSUR frequency)

The PSUR submission frequency is amended from 5 years to 2 years.

All MAHs of leuprorelin-containing depot products are requested to provide detailed analysis of all reported MEs cases in future PSURs, including information on whether follow-up of these cases was successful. This analysis will also serve as a measurement of effectiveness of risk minimisation measures resulting from this referral procedure where applicable.

### 5.1.2. Follow-up of cases

When a report of medication (handling) error with leuprorelin-containing depot product is received, all MAHs should perform an appropriate follow-up, regardless of whether the error was associated with adverse reaction(s) by following recommendations provided in the Good practice guide (EMA/762563/2014) on recording, coding, reporting and assessment of MEs. Follow-up of medication error cases should be considered as a routine pharmacovigilance activity through which MAHs should try to obtain relevant information not provided in the initial report.

## *5.2. Risk minimisation measures*

### 5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information (PI) are essential in order to minimise the risk of medication errors associated with the use of leuprorelin-containing depot medicinal products.

Eligard

The MAH Astellas should amend the sections 4.2 and 4.4 of the SmPC of Eligard 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. In cases of suspected or known handling error, patients should be monitored appropriately

Lutrate Depot (and associated names)

The MAH GP-Pharm should modify the packaging of the product in order to facilitate the access to instructions for use for healthcare professionals and update the section 6.6 of the SmPC of Lutrate Depot to provide more clear instructions for the product preparation.

All leuprorelin-containing depot medicinal products

Section 4.2 of the SmPC and section 3. of the PL of all leuprorelin containing depot medicinal products should be updated to include the statement that the product should be handled, prepared and administered only by healthcare professionals who are familiar with these procedures.

### 5.2.2. Direct Healthcare Professional Communication/Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) needs to be disseminated to raise awareness of the potential of MEs and highlight that the instructions for reconstitution should be strictly followed. The DHPC should be distributed to physicians who are usually prescribe these products and to all other HCPs (such as nurses) involved in preparation, reconstitution and administration of the products as per national clinical practice. The communication is to be sent in accordance with the agreed communication plan.

# 6. Condition to the marketing authorisations

The marketing authorisation holder Astellas shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

| | |
|---|---|
| The MAH Astellas should replace the current Eligard drug device combination product with a new one (e.g. containing two pre-connected syringes) with the objective of reducing the risk of medication errors. Relevant supportive documentation including adequate usability data should also be provided. | The corresponding regulatory procedure should be submitted to the relevant National Competent Authorities for assessment by 31 October 2021. |

# 7. Grounds for Recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for leuprorelin-containing depot medicinal products.
- The PRAC considered the totality of the data submitted for leuprorelin-containing depot medicinal products with regards to medication errors, the discussion on the steps of the reconstitution process and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the marketing authorisation holders in writing as well as data obtained by a Eudravigilance analysis.
- The PRAC noted the established efficacy of the leuprorelin-containing medicinal products in their approved indications, if they are used in accordance with the terms of the marketing authorisation and administered correctly.
- The PRAC confirmed the risk of medications errors associated with the incorrect handling of the reconstitution and administration of these medicinal products. The PRAC noted that these medication errors might lead in some cases to underdosing and consequently a lack of efficacy.

- The data indicates that products which require a higher number of reconstitution steps in their preparation and administration have a higher risk of medication errors.
- For Eligard, the product with the highest number of reconstitution steps, medication errors continue to be reported despite the multiple risk minimisation activities in place. The PRAC considered that the most effective measure to minimise medication errors is to replace the administration device with a new one requiring fewer reconstitution steps. The PRAC further considered that until the new administration device for Eligard becomes available, there is the need to highlight to HCPs that the instructions for reconstitution and administration must be strictly followed, by updating the product information.
- The PRAC noted that most of the medication errors reported for the products of GP-Pharm and affiliated MAHs (Lutrate Depot and associated names) concern a specific step of the preparation process, and concluded that the product information should be revised to clarify the instructions for this step and the packaging of the product should be modified in order to facilitate the access to instructions to HCPs.
- In view of the number of reported medication errors performed by patients, given the complexity of the reconstitution process of the leuprorelin-containing depot medicinal products, the PRAC was of the view that leuprorelin-containing depot medicinal products should not be self-administered and only be prepared and administered by HCPs who are familiar with these procedures.
- The PRAC agreed that medication errors resulting in lack of efficacy should be monitored as a safety issue of special concern through PSURs and should be added as an important identified risk in existing RMPs. The PSUR submission frequency should be revised from 5 years to 2 years.
- The PRAC also agreed on the dissemination of a direct healthcare professional communication, together with a communication plan.

In view of the above, the Committee considers that the benefit-risk balance of leuprorelin-containing depot medicinal products remains favourable subject to the agreed conditions to the marketing authorisations and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for leuprorelin-containing depot medicinal products.

The conditions imposed to the marketing authorisation of Eligard are set out in section 6 of this report.