VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Prostate cancer is the most common cancer among men in the US and Europe. In patients whose cancers are aggressive or advanced, treatments include surgical removal of the prostate, radiation therapy and more commonly treatment reducing the male hormone. Risk factors for prostate cancer include age, race/ethnicity, and family history. Prostate cancer tends to affect older men. Compared to White men, Black men are 1.6 times more likely to

develop prostate cancer and 2.5 times more likely to die from it. White men, however, are more likely than men of Asian descent or Hispanic ethnicity to develop prostate cancer. The likelihood of developing prostate cancer more than doubles for a man whose father or brother has been affected by this disease. Studies suggest that strong familial predisposition may be responsible for 5-10% of prostate cancers. Also, specific dietary factors (i.e., excessive consumption of fat from animal sources, such as red meat or high-fat dairy products) may be linked to a slightly higher risk for prostate cancer.

VI.2.2 Summary of Treatment Benefits

Eligard for treatment of advanced prostate cancer.

ELIGARD active substance (leuprorelin acetate) belongs to the group of so-called gonadotropin releasing hormones. These medicines are used to decrease the production of certain sex hormones (such as testosterone). ELIGARD is used to treat advanced prostate cancer that is dependent on testosterone in adult men, and it has been used in clinical practice for many years

In a clinical study with Eligard, all patients who received the full dose of 22.5 mg had their testosterone reduced to very low levels after 5 weeks. Prostate-specific antigen (PSA) levels decreased by 98% over 6 months. PSA is a biological marker used for monitoring prostate cancer.

The clinical study AGL 9904, in which 120 patients with advanced prostate cancer were evaluated during a six-month treatment period, demonstrated that 94% of patients achieved castrate level suppression (decrease of testosterone to very low levels) by Day 28 and 98% by Day 35; all remained suppressed throughout the study. There was also improvement of the symptoms (bone pain, problems passing urine).

The clinical study, AGL 9909, in which 117 patients with advanced prostate cancer were evaluated during a six-month treatment period, demonstrated that 98% of patients achieved castrate suppression by Day 28, and 99% by Day 35 of treatment. There was also improvement of the symptoms (bone pain, problems to pass urine).

Long-term studies have shown that continuation of therapy with ELIGARD maintains testosterone below the castrate level (very low levels of testosterone) for up to 7 years, and presumably indefinitely.

Eligard in combination with radiotherapy for treatment of high risk localized and locally advanced prostate cancer patients.

Research has demonstrated that there is no difference in risk/benefit between the various drugs that reduce the male hormone level and between various products similar to Eligard.

Studies have shown that there is an advantage when treatments such as Eligard are used together with radiotherapy in patients with high risk localised and locally advanced prostate cancer. Leading professional societies in the field recommend this combination therapy.

VI.2.3 Unknowns Relating to Treatment Benefits

A small proportion of patients will have tumours that are 'castration-resistant', meaning that even if testosterone (male hormone) is reduced the tumours may continue to grow or spread to other parts of the body. Approximately 5-10% of prostate cancer patients did not reach low levels of testosterone following treatment with a product similar to Eligard.

No studies have been done to investigate the use of Eligard in other indications for which products similar to Eligard are commonly prescribed such as endometriosis (illness affecting women) or precocious puberty. Treatment benefit has not been studied in children or patients with kidney or liver impairment.

VI.2.4 Summary of Safety Concerns

Table 43: Important Identified Risks

Risk	What is Known (Including Reason Why it is Considered an Identified Risk)	Preventability
Osteoporosis (thinning of the bones)	There is an increased risk of osteoporosis (thinning of the bones) and fracture in patients undergoing treatment for reducing the male hormone level. It is recommended that: ● Healthcare professionals should be aware of these potential safety issues and carefully weigh the benefits and risks of the use of Eligard and products similar to Eligard when determining treatment. ● Patients receiving Eligard or products similar to Eligard should be monitored for development of osteoporosis and fractures. ● Health care professionals should manage osteoporosis risk factors for patients, such as corticoid therapy use, chemotherapy use and osteoporosis drug use and anticoagulant (blood thinning medicine) use, according to current clinical practice. ● Patients should not stop their treatment with Eligard or products similar to Eligard unless told to do so by their healthcare professional.	Increased exercise, calcium and vitamin D supplements, and medications such as denosumab (human antibody to treat osteoporosis) protect the bone. Additionally, medications belonging to the group of so-called bisphosphonates (such as pamidronate, alendronate or zoledronic acid) increase the density of the bone in the hip and spine. Use of a bisphosphonate in combination with a gonadotropin-releasing hormone (GnRH) agonist may reduce bone loss.

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Table 43: Important Identified Risks

Risk	What is Known (Including Reason Why it is Considered an Identified Risk)	Preventability
Flare effect including ureteric obstruction and spinal cord compression (worsening of the symptoms including blockage of urine passage and compression of the spine)	There's a risk of clinical flare (worsening of the symptoms) at the start of treatment with Eligard and other products similar to Eligard. This risk occurs during the first 3 to 4 weeks after the start of the treatment. ● Healthcare professionals should be aware of these potential safety issues and carefully weigh the benefits and risks of use of Eligard and products similar to Eligard when determining treatment. ● Patients receiving Eligard or products similar to Eligard should be monitored for worsening of symptoms at the start of treatment. ● Health care professionals should manage clinical flare risk factors especially in patients with pre-existing spinal bone injuries or urine passage blockage, according to current clinical practice. ● Patients should not stop their treatment with Eligard or products similar to Eligard unless told to do so by their healthcare professional.	Treatment with medication belonging to the group of so-called antiandrogens during GnRH treatment initiation reduces the risk of worsening of the symptoms. Concomitant therapy with an anti-androgen decreases the incidence of flare effect, but does not completely prevent its occurrence. It is recommended that antiandrogen therapy precede or be co-administered with GnRH agonist and be continued in combination for at least 7 days.

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Table 43: Important Identified Risks

Risk	What is Known (Including Reason Why it is Considered an Identified Risk)	Preventability
Lack of efficacy due to medication error (lack of efficacy due to incorrect preparation and/or administration of Eligard)	There have been reports of medication errors with Eligard (incorrect or wrongful preparation and/or administration), some of which described lack of efficacy. Eligard should only be given by a healthcare professional familiar with proper preparation procedures. It is recommended that: ● Healthcare professionals should be aware of this potential safety issue. ● Patients receiving Eligard or products similar to Eligard should have their testosterone levels monitored in case of a suspected or known medication error in order to assess treatment efficacy. ● Patients should not stop their treatment with Eligard or products similar to Eligard unless told to do so by their healthcare professional. ● Product should not be given if it was not properly prepared.	The Package Leaflet in Section 7 describes in detail the proper technique for preparation and reconstitution of Eligard. As stated in the Package Leaflet, Eligard should only be administered by a doctor or a nurse; if the product is not prepared using the proper technique, it should not be administered as lack of clinical efficacy may occur due to incorrect reconstitution of the product.

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Table 43: Important Identified Risks

Risk	What is Known (Including Reason Why it is Considered an Identified Risk)	Preventability
Diabetes/ changes in glucose tolerance	There seem to be a small increased risk of diabetes in patients undergoing treatment for reducing the male hormone. However, this has not been confirmed. It is recommended that: ● Healthcare professionals should be aware of these potential safety issues and carefully weigh the benefits and risks of use of Eligard and products similar to Eligard when determining treatment. ● Patients receiving Eligard or products similar to Eligard should be monitored for development of diabetes. ● Health care professionals should manage cardiovascular risk factors for patients, such as smoking and increases in blood pressure, cholesterol, blood sugar, and weight, according to current clinical practice. ● Patients should not stop their treatment with Eligard or products similar to Eligard unless told to do so by their healthcare professional.	Blood glucose and/or glycosylated hemoglobin (HbA1c) (a biological marker for the effectiveness of diabetes treatment) should be checked periodically when receiving a GnRH agonist.
Pituitary apoplexy (loss of blood supply to the pituitary gland)	These are rare cases termed as pituitary apoplexy, which have been reported in other drugs which have a mechanism similar to Eligard. Symptoms such as sudden headache, vomiting, altered mental status and sometimes heart collapse, appearing within two weeks of taking Eligard, should be reported to the healthcare professional.	Medical advice should be sought if symptoms such as sudden headache, vomiting, altered mental status and sometimes heart collapse occur.

Table 44: Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)	Preventability
Cardiovascular (heart and blood vessels) diseases	There have been reports of cardiovascular events in patients taking Eligard or products similar to Eligard but it is unknown if these events were caused by these products. It is recommended that: ● Healthcare professionals should be aware of these potential safety issues and carefully weigh the benefits and risks of use of Eligard and products similar to Eligard when determining treatment. ● Patients receiving Eligard or products similar to Eligard should be monitored for development of cardiovascular disease. ● Health care professionals should manage cardiovascular risk factors for patients, such as smoking and increases in blood pressure, cholesterol, blood sugar, and weight, according to current clinical practice. ● Patients should not stop their treatment with Eligard or products similar to Eligard unless told to do so by their healthcare professional.	Regular check-up of heart and blood vessels is recommended when receiving gonadotropin-releasing hormone (GnRH) agonists

Table 30: Missing Information

Risk	What is Known (Including Reason Why it is Considered Missing Information)
Use in children	The efficacy of Eligard in patients younger than 18 years-old has not been evaluated. Eligard is not to be used in children.
Use in patients with hepatic (liver) impairment	No clinical studies were performed in patients with liver impairment.
Use in patients with renal (kidney) impairment	No clinical studies were performed in patients with kidney impairment.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) that provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay

language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This product has risk minimisation measures in addition to the SmPC and PL. These additional risk minimisation measures are for the following risk: Lack of efficacy due to medication error (lack of efficacy due to incorrect preparation and/or administration of Eligard); see [Table 45].

Table 45: Additional Risk Minimisation Measures: Lack of Efficacy Due to Medication Error

Risk minimisation measure	**Letter to healthcare professionals who administer or prescribe Eligard**
Objective and rationale	• To make healthcare professionals who administer or prescribe Eligard aware that handling errors have occurred during Eligard use, and that lack of efficacy is possible if Eligard is given to a patient after being incorrectly prepared. • To make healthcare professionals aware that the patient's testosterone (male hormone) levels should be checked if it is suspected that Eligard was given after incorrect preparation.
Proposed action	A letter was sent to health professionals in Europe in November/December 2014, informing them that: • Lack of clinical efficacy may occur if Eligard is not properly prepared; • Medication errors related to improper storage and preparation of Eligard have occurred; • Proper preparation of Eligard is important for safe and effective treatment of prostate cancer patients; • Healthcare professionals who administer Eligard must be familiar with, and follow, the instructions for proper preparation of Eligard; • Eligard must be prepared when it is at room temperature; • A patient's testosterone (male hormone) level should be checked if it is suspected that Eligard was given after incorrect preparation.
Risk minimisation measure	**Educational materials that provide instructions on proper preparation of Eligard**
Objective and rationale	To provide supplementary information to healthcare professionals regarding the instructions for proper preparation of Eligard. This may reduce the number of handling errors related to Eligard and the risk of lack of efficacy.
Proposed action	Instructional poster and instructional video (delivered by USB flash drive, smart phone application, and hosted website) will be distributed and/or made available to healthcare professionals who administer or prescribe Eligard.

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Table 45: Additional Risk Minimisation Measures: Lack of Efficacy Due to Medication Error

Risk minimisation measure	**Re-training of healthcare professionals who report problems or handling errors with Eligard**
Objective and rationale	To provide re-training for healthcare professionals who report product complaints or medication errors. This may reduce the number of handling errors related to Eligard and the risk of lack of efficacy.
Proposed action	Initiate face-to-face training on the proper preparation of Eligard for healthcare professionals who report product complaints or medication errors with Eligard.
Risk minimisation measure	**Device modification**
Objective and rationale	The device will be modified so that it will be impossible to remove the blue plunger rod without removing the grey stopper. This change may reduce the number of handling errors related to Eligard use and reduce the risk of lack of efficacy.
Proposed action	A proposal for this change was submitted in December 2014.
Risk minimisation measure	**Allow product to be stored at room temperature for up to 1 month**
Objective and rationale	This may reduce the number of handling errors related to improper storage and use of the product before it has been brought to room temperature.
Proposed action	A proposal for this change was approved on 03 December 2014.
Risk minimisation measure	**Change in product presentation with fewer and easier handling steps**
Objective and rationale	To reduce risks of wrong product reconstitution and administration, a new product presentation with fewer and easier handling steps is being developed.
Proposed action	A proposal for a new product presentation with fewer and easier handling steps was submitted in December 2014. A feasibility study of the new product presentation is planned, with results due by October 2015.

VI.2.6 Planned Post Authorisation Development Plan

Not applicable to the current version of the RMP.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Version	Date	Safety concern	Comment
1.0	October 2014	Important identified risks: None Important potential risks: Pituitary apoplexy, Cardiovascular diseases and Diabetes/ changes in glucose tolerance Missing information: None	Not applicable.
2.0	April 2014	Same as for version 1.0.	No changes to safety concerns.
3.0	August 2014	Important identified risks: Osteoporosis, Flare-effect including ureteric obstruction and spinal cord compression, and Medication error. Pituitary apoplexy and Diabetes/ changes in glucose tolerance Important potential risks: Cardiovascular diseases Missing information: Use in children, Use in patients with hepatic impairment and Use in patients with renal impairment	Update to the safety specification of the Eligard RMP included new important identified risks: Osteoporosis, Flare effect including ureteric obstruction and spinal cord compression, and Medication errors were added as new important identified risks. Pituitary apoplexy and Diabetes/changes in glucose tolerance were re-categorized as important identified risks. Use in children, Use in patients with hepatic impairment and Use in patients with renal impairment were added as missing information.
4.0	October 2014	Same as for version 3.0	No changes to safety concerns.
5.0	December 2014	Important identified risk: Lack of efficacy due to Medication error Other safety concerns same as for version 4.0.	Update to the safety specification of the Eligard RMP included the change of the important identified risk from "Medication errors" to "Lack of efficacy due to medication error." Pharmacovigilance activities (i.e., monitoring product complaints and AE reports of medication error targeted data questionnaire) were added for this risk. Pharmacovigilance activities to assess effectiveness of risk minimisation measures for this risk were added. Risk minimisation measures for this risk were added, including updates to product information (SmPC, PL), additional educational materials (e.g., poster, video), and a plan for a new product presentation with fewer and easier handling steps, including a feasibility study.
6.0	March 2015	Same as for version 5.0	No changes to safety concerns.

6.1	June 2016	Update of section V.1 Risk Minimisation Measures by Safety Concern to include the following: • Process indicators for the educational materials • Success criteria for the process indicators • Outcome indicators for the educational materials	Request from BfArM to update the EU RMP with process and outcome indicators for the educational materials (poster, video, smart app and website).
6.2	Oct 2016	Update of section V.1 Risk Minimisation Measures by Safety Concern to include the following: • Process indicators for the educational materials • Success criteria for the process indicators • Outcome indicators for the educational materials	Response to the second request for supplementary information from BfArM regarding the update to the process indicators for the educational materials.