



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Leuprorelin

Proprietary Product Name: Eligard

Sponsor: Mundipharma Pty Ltd

September 2018

TGA Health Safety
Regulation

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADT	Androgen deprivation therapy
ASTRO	American Society for Therapeutic Radiology and Oncology
CCDS	Company Core Data Sheet
CTCAE	Common Terminology Criteria for Adverse Events
DRE	Digital rectal examination
DVH	Dose-volume histogram
EBRT	External beam radiotherapy
EUS	Endorectal ultrasound
HRPC	Hormone-refractory prostate cancer
LENT / SOMA score	Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic scale
LBS	Literature Based Submission
MRT	Intensity-modulated radiotherapy
NCCN	National Comprehensive Cancer Network
NHT	Neoadjuvant hormonal treatment
OS	Overall Survival
PBRER	Periodic Benefit Risk Evaluation Report
PFS	Progression free survival
PS	Performance status (Karnofsky)
PCSM	Prostate-cancer-specific mortality
PCSS	Prostate-cancer symptom scale
SRR	Safety-related request
TAB	Total androgen blockade

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	6 October 2017
<i>Date of entry onto ARTG</i>	12 October 2017
<i>ARTG numbers:</i>	97449 (7.5 mg), 97450 (22.5 mg), 97451 (30 mg), 101581 (45 mg)
<i>Active ingredient:</i>	Leuprorelin
<i>Product name:</i>	Eligard
<i>Sponsor's name and address:</i>	Mundipharma Pty Ltd ¹ GPO Box 5214 Sydney NSW 2001
<i>Dose form:</i>	Modified release injection syringe
<i>Strengths:</i>	7.5 mg, 22.5 mg, 30 mg, 45 mg
<i>Approved therapeutic use:</i>	Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy
<i>Route of administration:</i>	Subcutaneous
<i>Dosage:</i>	The dosage is essentially 7.5 mg a month. The differing doses represent differing times between dosing.

Product background

This AusPAR describes the application by the sponsor to extend the indications for leuprorelin (tradename: Eligard). Leuprorelin was originally registered in 2003 in 7.5 mg, 22.5 mg and 30 mg doses for modified release injection and a 45 mg dosage was approved in 2005. Leuprorelin is currently approved for the following indication:

Palliative treatment of advanced prostate cancer

This submission seeks an extension of indication, specifically:

Treatment of high-risk, localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

The drug is a synthetic nonapeptide analogue of gonadotropin releasing hormone (GnRH) which when used interrupts the natural pulsatile stimulation of GnRH receptors and thus desensitises them, resulting in decreased natural pituitary gonadotropin secretion and suppressed testicular and ovarian steroidogenesis.

¹ At the time of the submission of the application the sponsor was Tolmar Australia Pty Ltd.

Prostate is the second most common cancer in men. It is estimated there were 1,100,000 cases world-wide in 2012 and 307,000 deaths. For men with newly diagnosed disease, factors in treatment selection include:

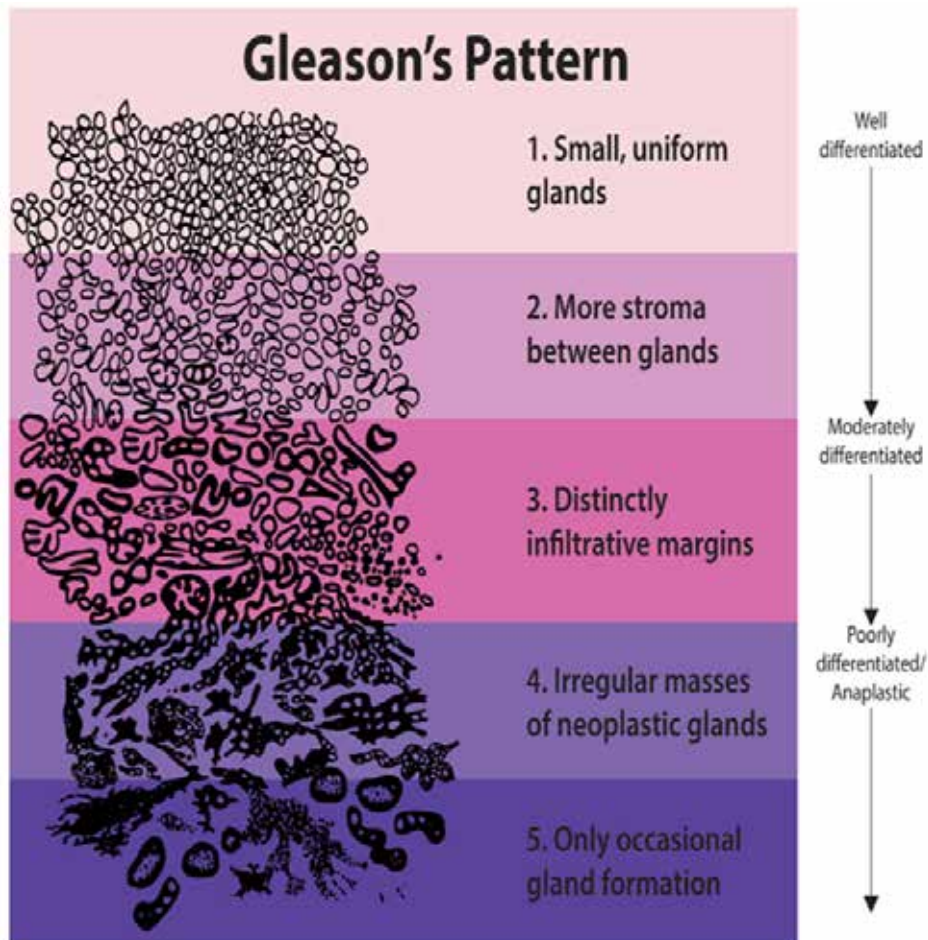
- Extent of disease (TNM staging), tumour size and extent, nodes, metastases
- Grade (Gleason score)
- PSA level
- General medical condition of the patient
- The potential complications with each treatment

TNM staging and Gleason group grading: the standard system for this is that of the American Joint Committee of Cancer (AJCC)/International Union Against Cancer (UICC). The Gleason group grading is based upon architectural features and correlates with clinical behaviour. A higher score indicates likelihood of both disease outside the prostate and worse outcome after treatment. The 'score' is derived from adding the two most prevalent differentiation patterns, i.e. if a biopsy has predominantly grade 3 and some grade 4 disease, the score is 7. It is a key component of the TNM grading system. The new 'Grade group' gives a more accurate risk stratification as it shows increasing risk of biochemical recurrence and prostate cancer mortality with increasing Grade:

- Grade group 1: Gleason score ≤ 6
- Grade group 2: Gleason score $3 + 4 = 7$ (hazard ratio (HR) 1.9 relative to Grade group 1)
- Grade group 3: Gleason score $4 + 3 = 7$ (HR 5.4 relative to Grade group 1)
- Grade group 4: Gleason score = 8 (including $4 + 4 = 8$, $3 + 5 = 8$, or $5 + 3 = 8$; HR 8.0 relative to Grade group 1)
- Grade group 5: Gleason scores 9 to 10 ($4 + 5$, $5 + 4$, or $5 + 5$; HR 11.7 relative to Grade group 1)

Examination, PSA, Gleason score, number of positive biopsy cores and imaging determine clinical staging.

The Gleason score is determined by biopsy appearance as shown in Figure 1.

Figure 1: TMN Staging and Gleason Grade

The PI does not specify criteria for high-risk, localised or locally advanced prostate cancer. Hence as the PI stands, this would be the judgement of prescribers based upon the clinical literature.

For those with clinically localised, high risk disease (pertinent to this submission), these include patients with presumed extra-prostatic extension on digital rectal examination; serum PSA ≥ 20 ng/mL, or; a Grade Group of 4 or 5 (Gleason Score 8 to 10). Treatment options include external beam radiotherapy with or without brachytherapy, or radical prostatectomy. Radical prostatectomy is limited to patients without fixation of their primary tumour. Long term androgen deprivation therapy (ADT) is indicated for:

- Those having external beam radiation as primary therapy (combine for 2 to 3 years), and;
- If radiotherapy added as a combination of external beam therapy and brachytherapy, a 12 month course of ADT as well.

Adjuvant ADT appears to decrease cancer-specific mortality, as well as biochemical recurrence and distant metastases in men with positive nodes at radical prostatectomy.

Regulatory status

At the time of this submission to the TGA, the international regulatory status was as is shown in Table 1.

Table 1: International regulatory status at the time of this submission to TGA

Country	Product Name	Submission Date	Current Status	Approval Date	Approved Indications
EU (including the Netherlands and Sweden)	Eligard 7.5 mg, 22.5 mg, 45 mg	13 August 2013	Approved	29 August 2014	Treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline

Description	Date
Submission dossier accepted and first round evaluation commenced	30 September 2016
First round evaluation completed	5 April 2017
Sponsor provides responses on questions raised in first round evaluation	24 May 2017
Second round evaluation completed	29 May 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	27 June 2017
Sponsor's pre-Advisory Committee response	14 July 2017

Description	Date
Advisory Committee meeting	4 August 2017
Registration decision (Outcome)	6 October 2017
Completion of administrative activities and registration on ARTG	12 October 2017
Number of working days from submission dossier acceptance to registration decision*	221

* Legislative timeframe is 255 working days

III. Quality findings

Introduction

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Contents of the clinical dossier

The applicant has prepared a LBS to support the proposed indication. Eligard has been approved in several countries, including Australia, for the palliative treatment of advanced prostate cancer for greater than 10 years. This application therefore meets the requirements of the TGA Guideline for a LBS.

The TGA-approved search strategy does not include nonclinical studies due to the wealth of bridging data available from the literature. No additional nonclinical studies would be required, and therefore only a justification is provided.

There are no other changes proposed for the approved Australian PI, other than those detailed in this application. That is, the pre-existing indications, dosage form and regimen, route of administration, and formulation remain unchanged.

The sponsor provided the following additional administrative information:

- 2 minor variations (a Self-Assessable Request/ Minor Editorial Changes to the PI, and a safety related request (SRR)) for the Eligard products.

- Many of the PI changes submitted are the same changes proposed in the PI submitted during pre-submission. The PI in this application has been annotated where a change has already been submitted during these minor variations.
- The periodic benefit-risk evaluation report (PBRER) provided in this application is for the period: 21 July 2014 - 20 May 2015. As a result, TGA might expect lodgement of further relevant data:
 - Tolmar is expecting the next PBRER, and subsequent Company Core Data Sheet update, to be available around October 2016. As a result, there may be safety updates to the PI at the appropriate milestone.

The sponsor submitted SmPC for Eligard from the EU, and the PI document of another LHRH agonist registered in Australia; goserelin (Zoladex). An evaluation report for Eligard from the EU has also been submitted dated 28 August 2014; however, this report is based on different dataset.

- The literature search identified 3 literature reports which support the safety and efficacy; 5 literature reports supporting the efficacy; and 5 reports supporting the safety of leuprorelin acetate injections in the extension of indication sought in this application.

The submission included:

- 2 pivotal studies (NHMRC level 2 evidence) of efficacy and safety (Mottet 2012, Widmark 2009) and 1 study of efficacy with similar hierarchy of evidence (Solberg 2013) in which participants received leuprorelin at half of the dose currently registered, with the duration of leuprorelin treatment ranging from 3 months to 3 years.
- The rest of the studies included represented lower level of evidence (NHMRC level III or IV).
- All studies included in the dossier were open-label studies. Only the efficacy/safety study by Mottet 2012 utilised leuprorelin treatment for any substantial length of time (3 years) in neoadjuvant and adjuvant setting. The rest of the studies, including those labelled 'level II evidence' used nonsteroidal antiandrogen (that is, flutamide) long term, following leuprorelin given in neoadjuvant setting to curative radiotherapy.
- 2 safety studies with 'level II evidence' were the extensions of the original Widmark 2009 trial and the comments on leuprorelin dosage and long term antiandrogen use equally apply here.
- The sponsor summarised the safety data:

Safety data provided in this application has been collected from 2313 patients who have received leuprorelin acetate in doses ranging from 3.75 mg per month to 22.5 mg every 3 months, administered as SC or IM for between 3 months to 18 years.

Active comparators to leuprorelin have not been used in the studies. The treatments included curative radiotherapy administered with or without androgen deprivation therapy; that in many instances involved long-term nonsteroidal antiandrogen, not leuprorelin or other GnRH agonist. A total of 9 of these studies compared the combination to leuprorelin or radiotherapy alone.

Pharmacokinetics

No new data presented.

Pharmacodynamics

No new data presented.

Dosage selection for the pivotal studies

No new data presented.

Efficacy

Studies providing efficacy data

Pivotal studies (NHMRC level II of evidence)

Mottet 2012²

Prospective, multicentre, open-label, randomised, efficacy and safety study comparing 3 year androgen deprivation therapy (ADT) + radiotherapy (RT) with ADT alone in locally advanced prostate cancer patients (n = 264).

Widmark 2009³

Open label, randomised, multicentre study assessing the effect of radiotherapy in locally advanced prostate cancer patients (n = 875) by comparing endocrine therapy with and without RT, followed by castration on progression.

Solberg 2011⁴

This prospective sub-study to the Scandinavian Prostate Cancer Group-7 (SPCG-7) study by Widmark 2009 evaluated the incidence and clinical implications of residual prostate cancer in post-treatment prostate biopsy specimens.

Supportive studies

Nguyen 2013⁵ (NHMRC level III-2)

A retrospective analysis reporting on the long-term outcomes of high-risk prostate cancer patients (n = 741) treated with low or high dose EBRT with or without ADT at a single tertiary institution.

Stone 2000⁶ (NHMRC level III-2)

Retrospective study comparing the effect of neoadjuvant hormonal therapy with leuprolide and flutamide on prostatic biopsy findings in patients (n = 296) receiving trans-perineal prostate brachytherapy.

² Mottet N, et al. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol.* 2012 Aug; 62(2):213-9.

³ Widmark A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet.* 2009 Jan 24;373(9660):301-8.

⁴ Solberg A, et al. Residual prostate cancer in patients treated with endocrine therapy with or without radical radiotherapy: a side study of the SPCG-7 randomized trial. *Int J Radiat Oncol Biol Phys.* 2011 May 1;80(1):55-61.

⁵ Nguyen QN, et al. Long-Term Outcomes for Men With High-Risk Prostate Cancer Treated Definitively With External Beam Radiotherapy With or Without Androgen Deprivation. *Cancer* 2013; 119: 3265-71.

⁶ Stone NN, et al. Effects of neoadjuvant hormonal therapy on prostate biopsy results after (125)I and (103)Pd seed implantation. *Mol Urol.* 2000 Fall;4(3):163-8;discussion 169-70.

Studies with low level of evidence*Heymann 2007⁷ (NHMRC level IV)*

Prospective study evaluating the toxicity and efficacy of individualised neoadjuvant ADT ‘administered to maximal response’, followed by EBRT with continued ADT for a total of 9 months for clinically localised prostate cancer.

Stone 1999⁸ (NHMRC level IV)

Observational case series that analysed the effects of NHT on prostate volume (PV) prior to radioactive seed implantation, and the PSA and post-implant biopsy outcomes of high-risk patients (n = 145).

Zelevsky 1997⁹ (NHMRC level IV)

Uncontrolled case series that prospectively assessed the impact of NHT given prior to RT (3D CRT) based on the size of prostatic tumours in relation to normal tissue structures, and the response to treatment including late toxicity in patients with localised prostate cancer.

Evaluator’s conclusions on efficacy

The following is the summary of efficacy presented by the sponsor (represented as bullet points):

- The addition of NHT to RT results in a highly significant reduction in the risk of cancer progression, an improvement in locoregional control, metastasis free survival and absolute risk reduction in mortality.

The addition of RT to 3 years of ADT significantly reduces the risk of progression and improves locoregional control and metastasis-free survival in patients with locally advanced prostate cancer, however, longer follow-up is needed to assess the potential survival impact.

- The benefit in PFS did not translate into a survival advantage at 5 Years (Mottet 2012; NHMRC level II). NHT plus high dose RT produced highly significant improvements in biochemical disease free survival, prostate cancer specific survival and clinical & local failure rates over 5 and 10 year follow up.
- The long-term ADT (≥ 2 years) in combination with high-dose external beam radiation therapy produced significant improvements in biochemical, clinical, and survival outcomes, and local failure rates were low and associated symptoms were uncommon (Nguyen 2013; NHMRC level III). At 5 Years, 82 % (74 - 87 %) of patients treated with NHT and high dose RT remained alive with no disease, compared to 45.9 % (41 - 51%) of those patients treated with no NHT and low dose RT (Nguyen 2013; NHMRC level III).
- Patients receiving endocrine therapy only, had a 3 times higher incidence of local residual prostate cancer after treatment compared to those that received combined therapy.

⁷ Heymann JJ, et al. Phase II study of neoadjuvant androgen deprivation followed by external-beam radiotherapy with 9 months of androgen deprivation for intermediate- to high-risk localized prostate cancer. *J Clin Oncol.* 2007 Jan 1;25(1):77-84.

⁸ Stone NN, Stock RG. Neoadjuvant Hormonal Therapy Improves the Outcomes of Patients Undergoing Radioactive Seed Implantation for Localized Prostate Cancer. *Mol Urol.* 1999;3(3):239-244.

⁹ Zelevsky MJ, Harrison A. Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. *Urology.* 1997 Mar;49(3A Suppl):38-45.

Solberg found that patients receiving endocrine therapy only, had a three times higher incidence of local residual prostate cancer compared to those that received combined therapy ($p < 0.001$) (Solberg 2011; NHMRC level II).

- Endocrine therapy alone is a significant predictor of residual prostate cancer.

In logistic regression analysis, significant predictors of residual prostate cancer were as follows: endocrine therapy alone (OR 7.49 (3.18 - 17.7), $p < 0.0001$) and baseline PSA (OR 1.03 (1.00 - 1.07), $p = 0.044$). (Solberg 2011; NHMRC level II).

- Mean prostate volume (PV) reduction observed following 3 months of NHT was 35 % (50.4 - 31 mL) overall, but much larger in patients with large prostate glands (mean reduction 40 mL, 41 %) (Stone 1999; NHMRC level IV).
- The change in geometry of bulky prostate tumours in relation to normal tissue structures before and after 3 months of NHT, prior to RT, ranged from 18 % for rectum tissue to 100 % for small bowel (Zelefsky 1997; NHMRC level IV).
- Addition of ADT (2 or 3 years) to brachytherapy and EBRT is common in patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-free survival reaching 87 % and 91 %, respectively. However, it remains unclear whether the ADT component contributes to outcome improvement.
- The studies included in this application therefore adequately demonstrate that combined ADT and radiotherapy improves the management of high risk locally advanced and localised prostate cancer and reduces the risk of long term morbidity and mortality.

The highest level of evidence for efficacy data in this submission is represented by NHMRC level II of evidence.

This evaluator concludes that the presented data demonstrates that combined ADT plus RT improves the management of high risk locally advanced and localised prostate cancer, albeit at risk of increased morbidity. The data on mortality comes from studies with lower level of evidence.

The above statement relating to ADT in general could be extrapolated to leuprorelin, an LHRH agonist that was consistently administered in the neoadjuvant setting in 8 of the efficacy studies.

- Optimal ADT: LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.

The 2 pivotal studies in this submission used half of the recommended dose that is currently registered for leuprorelin, the fact that might have influenced efficacy, as well as the outdated radiotherapy regimens. Other deficiencies in the design of the outdated studies and the heterogeneous populations studied are addressed in relevant sections of this report.

The evaluator considers that it is appropriate not to specify within the indications if leuprorelin is to be used in neoadjuvant, or adjuvant setting, or concomitantly with radiotherapy. The prescriber would in such instances refer most likely to the current guidelines.

In conclusion, the evaluator is of the opinion that the presented efficacy data is sufficient to support the proposed extension of indication for Eligard. The statements for the Clinical Trials and the Adverse Effects sections need to be presented by the sponsor to reflect on the imperfections of data and the risks of the combination therapy.

The totality of presented data, including international guidelines and awareness of the current treatment practices, weighed heavily on this evaluator's conclusions.

Safety

Studies providing safety data

Background: The primary objective of the clinical safety component of the clinical data is to demonstrate that ADT when combined with RT has a risk profile appropriate to the therapeutic benefits achieved in high risk locally advanced and localised prostate cancer patients, and that acute and late toxicity is in line with that expected for either ADT or RT.

- Safety data are presented in 8 published reports submitted with this application; 2 of these reports are well designed RCT, and 1 an uncontrolled Phase II study, that have also been included. (Mottet 2012, Widmark 2009, Heyman 2007)

Studies by Mottet and Widmark used half of the leuprorelin dose currently registered, for 3 years and 3 months, respectively. Widmark and the subsequent studies employed long term nonsteroidal antiandrogen, given until progression or death.

- The 5 other studies include 2 RCT, which provide safety data based on the follow up of all or a subgroup of patients recruited originally to the study by Widmark 2009. A further follow up study based on a Widmark cohort, but using a non-randomised aged matched healthy subject comparator arm is also included as a well-designed, pseudo-randomised trial. (Fransson 2009, Lund 2013, and Berg 2009)
- The remaining 2 reports include 1 interrupted time series with a control group (III-2), and 1 uncontrolled observational study (IV). (Kohutek 2016, Pervez 2010)

Kohutek 2016 - level III evidence; Pervez 2010 - level IV evidence. Both studies report on leuprorelin used according to current dosing recommendations.

Overall 5 of the 8 studies submitted to support the safety evaluation of NHT and RT are categorised as RCT or pseudo-randomised trials. Although these studies were designed and powered based on a primary efficacy variable, or as follow up studies of such a trial, they provide also good quality evidence relating to the safety profile of this combined therapy, due to the carefully planned and designed methods used to record possible ADE or experiences.

The 5 RCTs and the retrospective analysis used an active control, leuprorelin and an antiandrogen (ADT) (flutamide or bicalutamide), compared to ADT and RT. The 2 uncontrolled studies did not have a comparator arm and have been included in the safety summary as they provide important safety information regarding the combination of ADT and RT.

- In all safety studies radiation was delivered by external beam radiotherapy (EBRT) and/or brachytherapy according to the standard practices at the time the study was conducted.
- Leuprorelin was administered as NHT, often together with an antiandrogen such as flutamide, prior to commencement of RT. The doses of leuprorelin, duration of administration, timing in association with RT, prostate cancer categorisation and the efficacy and safety outcomes assessed in each individual report are provided
- The dose of ADT may also have been determined by best practice standards at the time of the study.
- The dose of leuprorelin used in the Mottet study was consistent with the recommended dose regimen in Australia, however the dose of leuprorelin used in

Widmark and related studies was only half that currently recommended. This may result in a more favourable safety profile being established in these studies, although as they all compared combined NHT and RT to NHT alone, the potential impact can be assessed.

The above statement is incorrect. The 2 pivotal studies for this application (Mottet 2012 and Widmark 2009 including the resulting sub-studies) used half of the recommended dose of leuprorelin.

- All these studies recruited patients generally consistent with a 'high risk' prostate cancer diagnosis.

Mottet 2012 included a small but unspecified percentage classified as T4, however no patient was classified as N1. Widmark 2009, and the follow up studies utilising the original patient cohort or subset thereof (Fransson, Berg and Lund) included around 20-25 % patients with seminal vesicle involvement, which technically classifies these patients as T3b, meaning that these patients in a slightly higher risk category compared to the target population.

It is considered unlikely however that this fact will significantly impact on the safety assessment of this treatment.

Patient exposure

Safety data provided in this application has been collected from 2313 patients who have received leuprorelin acetate in doses ranging from 3.75 mg per month to 22.5 mg every 3 months, administered as SC or IM for between 3 months to 18 years.

Post-marketing data

The application includes current PBRER which provides additional safety data obtained worldwide for the period of 21 July 2014 - 20 July 2015.

The PBRER is based on adverse events (ADEs) reported from relevant clinical trials and post-marketing sources from the 87 countries in which leuprorelin acetate is registered. There were no withdrawals for any regulatory/marketing authorisation in any country during the reporting period.

The Company Core Data Sheet (CCDS) of May 2014 is the reference safety information (RSI) in effect at the beginning of this reporting period.

There were no changes to the RSI during the reporting period; however there are proposed changes in progress to align this document with SmPC and USPI amendments noted below.

In summary, these changes are the inclusion of wording on the effect of androgen deprivation therapy in general, on prolongation of the QT interval, and on the potential for lack of efficacy to be observed if Eligard is not correctly reconstituted.

The PRAC also recommended changes to the Special Warning, Interaction and Undesirable effects sections of the Eligard SmPC as a consequence of a potential association between the use of medicinal products used for androgen deprivation therapy and QT interval prolongation, due to low testosterone levels.

Both recommendations were based on consideration of EudraVigilance data, post marketing reports and literature cases.

A cumulative review of all cases concerning medication errors was performed by Tolmar, including a root cause analysis. The reports of lack of efficacy due to medication error,

specifically handling errors associated with improper storage, preparation, reconstitution, and/or administration of the product, were analysed.

Up to the cut-off date of 7 May 2015, a total of 1,483 cases worldwide were retrieved. Of these cases, 1,208 cases of handling errors were identified; most of these cases (99 %) were spontaneous reports and ≈ 87 % of these cases were reported from Europe; few cases (2 %) were reported as serious.

The most frequently reported root causes for the handling error were: syringe issues in which leakage was reported (476 cases), issues with the grey stopper including stopper left and difficulty removing the stopper (311 cases), and needle issues including connection problems or breakage (102 cases), and mixing issues (67 cases).

Consequently, the following regulatory actions were taken by the European licence holder:

- Lack of efficacy statement in SmPC
- Additional instructions for health professionals in the SmPC
- Direct healthcare professional communication and training measures.

The sponsor noted: The importance of correct reconstitution and administration of Eligard to the delivery of efficacious treatment will be reinforced to Australian prescribers and other relevant health care professionals (HCP) through the provision of the inclusion of an additional instructional leaflet in the product carton, separate to the PI. In addition, the Australian sponsor will provide demonstration kits which company representatives will use to assist in the training of HCP in the appropriate administration of the product. An instructional video will also be provided on the company's website.

A similar audit of the Tolmar safety data base found no cases of QT prolongation or torsades de pointes reported with the use of leuprorelin acetate in the global safety data base up to the time of the PRAC recommendation.

However, the SmPC and USPI have however been updated to include QT prolongation in 'Special warnings and precautions'. A similar safety change was recommended by FDA. An appropriate precaution is also included in the Australian PI.

During the period of the PBRER, the following safety concerns have been subject to ongoing pharmacovigilance activities.

Important identified risks

- Osteoporosis
- Flare effect including ureteric obstruction and spinal cord compression
- Diabetes/changes in glucose tolerance
- Pituitary apoplexy
- Medication errors

Apart from medication errors, there was no new information received during the reporting period for identified or potential risks.

Important potential risk

- Cardiovascular diseases

Missing information

- Use in patients with renal impairment
- Use in patients with hepatic impairment
- Use in children

Summary of post-marketing data

The PBRER concluded that the adverse event profile of leuprorelin acetate has been well established in both clinical studies and in post marketing experience. The product has not been withdrawn or suspended for a safety reason in any country. The safety data remains in accordance with the previous cumulative experience and with the current RSI (CCDS). The content of the report does not change the current positive benefit risk assessment of Eligard in its various presentation forms.

The report represents information based on 238,874 patient years of exposure, and consists of 31 serious ADEs collected from clinical trials and 2,415 ADEs from post marketing sources.

This report therefore adds significant support to the assessment of the safety and risk benefit profile of this medicine.

The CCDS which was in effect at the start of this reporting period included both the palliative treatment indication currently registered in Australia, as well as the extension of indication proposed in this application.

The PBRER therefore provides additional information relevant to both the safety and risk benefit of Eligard when used in the extension of indication proposed in this application.

Apart from lack of efficacy due to the wrong administration technique, there was no new information relevant to these important identified or potential risks detected during the current reporting period.

The conclusion provided in Benefit-Risk Analysis Evaluation section of the PBRER adequately reflects the impact of the information provided in this report on the risk benefit profile of Eligard.

The overall appraisal of the benefit risk profile for Eligard remains favourable for the approved indication and population (including the proposed extension of indication for Australia).

Review of safety data from worldwide sources during the period covered by the PBRER revealed no new clinically significant safety signals that warrant an immediate change to the reference safety information (RSI).

All known AEs with leuprorelin acetate are listed in the current CCDS and there are no new risks identified other than those currently listed in the CCDS of Eligard dated 20 May 2014.

The proposed Australian PI reflects the information contained in the CCDS.

Evaluator's conclusions on safety

Safety data has been extracted from the 8 published clinical reports submitted with this application, 3 of which were also included in the efficacy section.

The 8 studies used to provide safety data associated with combined ADT and RT included 4 RCTs; 1 pseudo-randomised CT; 1 interrupted time series with control study, and 2 uncontrolled observational studies.

Design of the studies: The dosage and population exposure in these studies is considered closely reflective of the target dosage and population proposed in this application. While any safety evaluation based on published literature is necessarily limited by the design of the study and the methods used to present safety material, the strengths of the studies submitted, such as the consistency of the treated patient populations, leuprorelin dosing schedules used and the wide range of outcomes used in evaluation of safety, ensure that this safety information provides valuable additional material to estimate the potential

safety implications of the use of leuprorelin in combination with radiotherapy for the treatment of high-risk localised and locally advanced prostate cancer.

Two of the reports are individual well-designed pivotal RCT which evaluate the efficacy and safety of the use of ADT + RT with ADT alone in locally advanced prostate cancer patients. Three of the reports are supplementary follow up reports based on sub-sets or the entire cohort studied in one of the pivotal RCTs, which provide additional insights into the safety and risk-benefit of the proposed combination therapy.

Two uncontrolled studies evaluating the toxicities of ADT in combination with RT were included in the evaluation. Of which, one study assessed the administration of ADT to maximal response prior to RT + ADT, while the other assessed the administration of ADT followed by dose escalation and hypofractionation of intensity-modulated RT in combination with ADT.

A further retrospective analysis investigated the impact of ADT on the incidence of cardiovascular events in prostate cancer patients treated with RT.

The risk classification of prostate cancer in patients recruited into these studies have varied over time, due to the evolving nature of medical research and treatment, however overall the populations exposure to the combination therapy is generally consistent with the current histological, symptomatic and PSA based classification of high risk prostate cancer.

The overall safety population therefore included a high proportion of patients who could be considered to have high-risk locally advanced and localised prostate cancer.

The randomised and pseudo randomised CTs used doses of leuprorelin at half the licenced dose, however all other studies either administered, or were assumed to administer, the recommended dose. The patient cohorts were consistent with the targeted patient population.

Safety was assessed using AEs reported or obtained during patient interview. Relevant safety information was also provided from QoL assessments, depression and anxiety scores and fatigue, including from the evaluation of individual symptoms used to consolidate these functional domain scores, which were indicative of adverse treatment outcomes.

Information was provided by Physician grading of anorectal symptoms, urinary, upper and lower GI and sexual function and anorectal physiology and anatomy.

The change in plasma concentrations of sex hormones was also studied. An assessment of cardiovascular events associated with combination therapy was also provided in an observational study.

Overall, these studies provide an appropriate foundation upon which an assessment of the risk benefit profile of leuprorelin and RT can be made in patients with high-risk localised and locally advanced hormone-dependent prostate cancer.

NHT effectively reduces the volume of normal tissue exposed to high radiation doses in the majority of treated patients and decreases the potential morbidity of therapy.

In patients with locally advanced or high-risk local prostate cancer, the addition of local radiotherapy to endocrine treatment significantly reduces long term *PCSM*, the risk of progression and improves locoregional control and metastasis-free survival and substantially decreases overall mortality compared with endocrine treatment alone.

Conclusions: Although addition of radiotherapy to endocrine treatment significantly increased some treatment-related symptoms, the overall risk benefit assessment strongly favours the combination of ADT and RT.

While patients treated with ADT alone generally had a lower incidence of adverse effects, the combination of ADT and RT has generally not resulted in excess toxicity.

Addition of ADT in the form of leuprorelin acetate to RT unequivocally results in increased range of acute and late toxicities, a fact that that needs to be reflected in the PI of Eligard (currently missing from the document).

Of particular relevance are conclusions from 2 safety studies:

- Berg 2009: Prostate cancer patients receiving both high-dose pelvic RT and long term antiandrogen should be informed about the considerably long-term risk of impaired sexual function and possible risk of reduced physical function and vitality. Further studies into the possible long-term cardiovascular toxicity due to increased serum oestradiol concentration associated with antiandrogens may be required.
- Kohutek 2016: This large single-institution analysis of patients treated with EBRT and brachytherapy revealed an association between ADT use and an increased risk of cardiovascular morbidity, both among men receiving ADT at the time of RT and those receiving generally longer courses of salvage ADT at the time of recurrence.

While ADT is often an essential part of prostate cancer treatment, the study suggests that efforts to mitigate cardiovascular risk are important to consider in all men receiving prostate RT and ADT.

The safety data from the pivotal studies is suboptimal, as the studies were not powered for safety, and utilised smaller leuprorelin dose than currently registered. The use of long-term anti-androgen complicated the risk assessment.

The long-term usage of LHRH agonists, leuprorelin included, and the presented post-market data provide reassurance that the safety profile of Eligard is reasonably known by now.

First round benefit-risk assessment

As per sponsor:

'The primary objective of the clinical safety component is to demonstrate that ADT when combined with RT has a risk profile appropriate to the therapeutic benefits achieved in high risk locally advanced and localised prostate cancer patients, and that acute and late toxicity is in line with that expected for either ADT or RT.'

The application is intended to extend the indication for leuprorelin acetate within the pre-existing approved target patient population, using the same formulation and dosage recommendations already registered for Eligard.

The application to register the additional indication, combining leuprorelin with radiotherapy, is supported by 13 published studies providing appropriate clinical data assessing the impact on the established safety and/or efficacy profile of the combination therapy in over 2300 high risk prostate cancer patients. Duration of exposure to leuprorelin in these studies has been up to 18 years; 9 of these studies compare the combination to leuprorelin or radiotherapy alone.

In addition, both local and international best practice guidelines and treatment reviews acknowledge the role of combined androgen deprivation therapy (ADT) and radiotherapy in high risk patients.

Furthermore, goserelin, another GnRH agonist, has been registered in Australia for over 20 years and has had a similar indication approved in Australia; adjuvant and neo-

adjuvant therapy in combination with radiotherapy for the management of locally advanced prostate cancer in men suitable for hormonal manipulation.

In addition, this application includes extensive additional clinical trial evidence confirming the established risk benefit profile of this product.

The published reports of RCT and other studies submitted in this application to support the efficacy and/or safety of leuprorelin acetate in combination with RT to treat high risk prostate cancer patients demonstrates that this treatment has a favourable risk benefit profile and may be approved for the proposed extension of indication:

Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

Evidence provided in this application has demonstrated that combined ADT with leuprorelin and radiotherapy:

- Results in a highly significant reduction in the risk of cancer progression, an improvement in locoregional control, metastasis free survival and absolute risk reduction in mortality compared to NHT alone.
- Provides a highly significant improvement in biochemical disease free survival, prostate cancer specific survival and clinical and local failure rates over 5 and 10 Year follow up compared to NHT alone.
- Results in 82 % (74 - 87%) of patients treated with NHT and high dose RT remaining alive with no disease, compared to 45.9 % (41 - 51%) of those patients treated with no NHT and low dose RT.
- Results in patients so treated demonstrating a three times lower incidence of local residual prostate cancer compared to those that receiving NHT alone.
- Results in mean prostate volume (PV) reductions of 35 % (50.4 to 31 mL) following 3 months of NHT prior to RT.
- Produces a change in geometry of bulky prostate tumours in relation to normal tissue structures before and after 3 months of NHT, prior to RT, resulting in lower volumes of rectal, bowel and small intestine tissue being exposure to radiation.
- Offset against the significant enhancement in efficacy, and as expected, the addition of leuprorelin based ADT has a clinically relevant impact on the overall safety profile of this treatment regimen.
- Combined NHT and RT produce a small but significant increase in moderate to severe late effects related to urinary and sexual function compared to NHT alone.
- Generally the incidence, but not the severity, of individual ADEs reported in the GI, GU and sexual function domains is greater in patients receiving combined NHT and RT treatment compared to NHT alone.
- When assessed by Physician symptom scoring and manography, patients treated with NHT and RT demonstrate some deterioration of anorectal function.
- While patients treated with NHT and RT generally had slightly lower physical health ratings, emotional and mental health was either equivalent to or slightly better than the aged matched controls when measured using validated QoL and related questionnaires.
- The 10-Year incidence of post-RT cardiovascular events was significantly greater among patients receiving ADT at the time of RT compared with patients treated with RT alone.

The following risk benefit conclusions can be drawn from these data:

- Individual studies submitted in this application indicate that ADT in combination with RT has superior efficacy compared to RT alone or ADT alone especially with respect to progression free survival, biochemical survival and/or overall survival.
- While patients treated with ADT alone generally had a lower incidence of adverse effects, the combination of ADT and RT has generally not resulted in excess toxicity.
- Overall, the QoL of patients receiving ADT and RT is similar to those patients receiving ADT alone.
- The PBRER does not change the current positive benefit risk assessment of leuprorelin acetate in its various presentation forms.
- The overall risk benefit assessment therefore strongly favours the combination of ADT and RT in patients with high risk locally advanced and localised prostate cancer. This conclusion is supported by the evidence provided in this application.

The evaluator concurs with the general risk-benefit assessment as presented by the sponsor in this application. The presented data demonstrates that combined ADT plus RT improves the management of high risk locally advanced and localised prostate cancer, albeit at risk of increased morbidity. See efficacy conclusions in this report.

The addition of leuprorelin based ADT to curative radiotherapy has a significant and clinically relevant impact on the overall safety profile that needs to be adequately presented in the PI.

The data included in this dossier is not all leuprorelin-specific, but extrapolated from other therapeutic approaches encompassing the ADT as a whole.

This approach is considered acceptable by this evaluator based on decades long use of ADT in clinical practice in this setting, including the use of LHRH agonists, and the obvious scarcity of the more specific data.

Prostate cancer, including the localised advanced hormone-dependent cancer is a heterogeneous disease, the fact obviously reflected in the populations studied in the papers. It is also a condition with clinically entrenched and time sanctioned therapies. All this is reflected in the scarcity of high quality, modern RCTs evaluating the evolving therapeutic approaches.

The evaluator is comfortable with the approach taken by the sponsor and the overall data presented to support the proposed of extension of indication for Eligard. The following has been recently written about the various therapies for localised prostate cancer:¹⁰

Introducing the topic of comparative effectiveness for prostate cancer treatments with a reminder of the disease's heterogeneity risks tautology. However, the profound variation both in this cancer's biology and its clinical course is increasingly widely recognized, while management alternatives for clinically localized prostate cancer have exploded. Available options now include active surveillance, multiple surgical approaches to prostatectomy, various forms of external-beam and interstitial radiation, and a growing list of energy ablative technologies. Each treatment option has its own efficacy rate as well as its own set of complications, side effects and financial costs.

Difficulties comparing these options, together with the high prevalence of the disease, led the Institute of Medicine to include localised prostate cancer among the top 25 priority conditions for future comparative effectiveness research.

¹⁰ Lavery HJ, Cooperberg MR. Clinically localized prostate cancer in 2017: A review of comparative effectiveness. *Urol Oncol.* 2017 Feb;35(2):40-41.

The sheer volume of possible treatment options, with their individual risks and benefits, can be confusing for patients and clinicians to research, understand and explain.

Further to an ongoing research on various treatment modalities for localised prostate cancer, a novel grading system, composed of Grade Groups 1 to 5, was lately developed intended to replace the time-honoured Gleason score. This is likely to be reflected in all modern clinical trials.

The system was first developed in 2013 at the Johns Hopkins Hospital and subsequently validated in a large multi-institutional and multimodal study, and presented at the 2014 International Society of Urological Pathology meeting. The system was accepted both by participating pathologists as well as urologists, oncologists, and radiation therapists.

First round recommendation regarding authorisation

Conclusions

The sponsor submitted an application to register additional indication for Eligard (leuprorelin acetate) products for the:

Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

The sponsor has prepared LBS to support the proposed indication; with focus on LHRH agonist leuprorelin acetate; however, the high quality evidence relating specifically to leuprorelin is lacking.

The evaluator is of the opinion that the presented efficacy data is sufficient to support the proposed in this submission extension of indication for Eligard.

In arriving at this conclusion, the evaluator considered data related specifically to leuprorelin acetate, as well as data extrapolated from other therapeutic approaches encompassing the ADT as a whole.

On assessing the overall risk/benefit for leuprorelin, the presented data demonstrates that combined ADT plus RT improves the management of high risk locally advanced and localised prostate cancer, albeit at risk of increased morbidity.

Therefore, the statements for the Clinical Trials and the Adverse Effects sections need to be included in the PI document to reflect on the imperfections of data and the risks of the combination therapy.

Recommendations

The evaluator recommends the approval of this submission from Tolmar Australia Pty Ltd to extend indication for Eligard (leuprorelin acetate) products for the:

Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

The approval of this submission is conditional upon the sponsor addressing the recommendations relating to the changes to the PI.

VI. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for an evaluation in a submission of this type.

Nonclinical

There was no requirement for an evaluation in a submission of this type.

Clinical

Pharmacology

Not applicable

Efficacy

The submission contains 2 pivotal studies (Mottet 2012 and Widmark 2009) and a further study (Solberg 2011), all considered level II evidence. There are ten other supportive papers of lower levels of evidence. All were gathered via a documented literature search protocol.

Mottet 2012 is considered the principal evidence in the submission. It was a prospective multicentre open label randomised study (n = 264) comparing 3 year ADT and radiotherapy with ADT alone in locally advanced prostate cancer (T3 to 4, N0; or pathologic T3 without nodes or mets). Patients were randomly assigned either leuprorelin 11.25mg SC depot injection every three months (n = 133), or the same depot plus radiotherapy (n=131). Flutamide (750mg daily) was given in the first month of ADT treatment). Radiotherapy was external beam, not brachytherapy, and was initiated within 3 months of randomisation for a median duration of 55 days (range : 48 to 85).

- Note those with Gleason Score 8 to 10 were only 16.8% of the ADT group and 24.1% in the ADT+RT group. Also, the dose of leuprorelin is half that of the PI. There was also significant dropout in the study; only 8 in the ADT group completed ADT as planned while 71 in the ADT+RT group completed treatment.

The primary endpoint was 5 year PFS via either biochemical or clinical assessment. Multiple secondary endpoints included OS.

- PFS: With a median follow-up of 67 months, 5-Year PFS Kaplan-Meier estimates were 60.9% for combined therapy vs. 8.5% with ADT alone (ASTRO; p < 0.0001), and 64.7% versus 15.4%, respectively, for Phoenix (p < 0.0011). American Society for Therapeutic Radiology and Oncology (ASTRO) and the newer Phoenix: definition (nadir plus 2 ng/mL) p1 publication).
- OS was 71.4% with combined therapy versus 71.5% with ADT alone; disease-specific survival was 93.2% versus 86.2% (not statistically significant).

The study demonstrated greatly improved PFS in combination with RT. A comparator of ADT+RT vs RT might have been more appropriate to quantify the benefit of leuprorelin, particularly as ADT is considered adjunctive to primary RT treatment. The dose used was half that in the PI, however this study shows data for prolonged use; something the other

studies do not. Furthermore it is not clouded by prolonged use of other agents such as flutamide. ADT alone is shown to be inferior which is hardly surprising, although overall survival was not statistically significantly different between groups.

Widmark 2009 was also an open label randomised study (n = 875) comparing ADT with (n = 436) and without (n = 439) RT, followed by castration on progression. Inclusion criteria broadly agreed with the proposed treatment population. Patients received ADT consisting of leuprorelin 3.75 mg a month or 11.25 mg for 3 months in addition to flutamide 750 mg daily. Leuprorelin was ceased after 3 months and flutamide continued to progression or death. At this point those in the RT group received 3D conformational RT.

The primary endpoint was prostate cancer specific mortality (PCSM) at 7 years of RT + ADT versus ADT alone. Inclusion criteria ensured likely survival of 10 years+ at randomisation. QoL was a patient centric secondary endpoint of note here.

The cumulative PCSM (at 7 Years) was reported as 9.9 % (95% CI 7.1 to 12.8%) in the endocrine group and 6.3 % (95% CI 3.9 to 8.6%) in the endocrine + RT group (difference 3.7 %; 0.0 to 7.4 %). The relative risk of cancer-specific death was 0.44 (0.30 to 0.66, $p < 0.0001$) in favour of the endocrine plus radiotherapy treatment group.

At the 4-year follow-up 340 of 399 (85%) men in the ADT group and 359 of 401 (89%) men in the ADT+RT group returned the questionnaire. No significant difference in global health and quality of life score was seen 4 years post-treatment.

The study shows the favourable outcome of cancer-specific mortality when ADT is combined with RT. The additional benefit compared to primary RT treatment is not known given the comparator was ADT alone. Leuprorelin was used for 3 months only, presumably as a method of shrinking tumour mass before irradiation. Concomitant use of flutamide with leuprorelin initially and long term is an unquantifiable factor in disease outcome in this study when trying to assess the contribution of leuprorelin alone. Dosing of leuprorelin was again half that proposed in the PI.

The final study this Delegate considers worthy of singling out is that of Nguyen 2013 (n = 741). Men with high risk prostate cancer (that is, $\geq T3$, Gleason score ≥ 8 or PSA ≥ 1 ng/mL) were treated with high or low dose external beam radiation, with or without ADT, at a single institution between 1987 and 2004.

Of these study subjects, 295 received ADT for over 2 years (R2-18 years) and consisted of either bilateral orchidectomy, or IM leuprorelin with or without bicalutamide. Median treatment for ADT was 2.9 years. No patient received less than 2 years of ADT. In addition, ALL patients were high risk. At 5 years, men who had not received ADT and had received radiation dose < 75.6 Gy had higher clinical local failure rates than those given ADT and radiation dose < 75.6 Gy (24.2% versus 0%, $p < 0.0001$). The corresponding 5- and 10-year biochemical failure-free survival rates were significantly better for patients treated with both ADT and higher radiation dose (82% and 77%, $p < 0.0001$):

Table 2: Outcomes at 5 and 10 years according to the use of ADT and high or low radiation dose

Outcomes	No ADT, Low Dose n = 375	ADT, Low Dose n = 122	No ADT, High Dose n = 71	ADT, High Dose n = 173	P
Biochemical disease-free survival rates, %					
5 y	45.9 (0.41-0.51)	82.7 (0.74-0.88)	73.9 (0.61-0.82)	82.0 (0.74-0.87)	<.0001
10 y	30.1 (0.25-0.35)	63.3 (0.53-0.72)	61.4 (0.47-0.72)	-	
Overall survival rates, %					
5 y	81.6 (0.77-0.85)	87.3 (0.80-0.92)	87.2 (0.77-0.93)	92.3 (0.86-0.95)	.0035
10 y	56.8 (0.51-0.61)	67.3 (0.57-0.75)	72.0 (0.59-0.81)	-	
Prostate cancer-specific survival rates					
5 y	93.3 (0.90-0.95)	95.5 (0.89-0.98)	96.9 (0.88-0.99)	96.1 (0.91-0.98)	.068
10 y	81.6 (0.77-0.85)	84.4 (0.75-0.90)	94.5 (0.83-0.98)	-	
Clinical failure-free survival rates					
5 y	66.6 (0.61-0.71)	90.3 (0.83-0.95)	87.7 (0.77-0.93)	92.1 (0.87-0.95)	<.0001
10 y	56.0 (0.50-0.61)	77.6 (0.68-0.84)	81.9 (0.69-0.89)	-	
Local failure rates					
5 y	24.2 (0.71-0.80)	2.7 (0.92-0.99)	9.4 (0.80-0.96)	0 (n/a)	<.0001
10 y	32.8 (0.62-0.72)	6.8 (0.85-0.97)	12.9 (0.76-0.93)	-	
Nodal failure rates					
5 y	4.7 (0.92-0.97)	4.5 (0.90-0.98)	1.6 (0.89-0.99)	2.5 (0.94-0.99)	.632
10 y	6.8 (0.90-0.96)	7.2 (0.85-0.96)	1.6 (0.89-0.99)	-	
Distant metastasis rates, %					
5 y	10.5 (0.86-0.92)	8.9 (0.84-0.95)	3 (0.89-0.99)	6.8 (0.88-0.96)	.081
10 y	17.7 (0.77-0.86)	19.2 (0.71-0.87)	5.5 (0.83-0.98)	16.1 (0.71-0.91)	

Abbreviation: ADT, androgen deprivation therapy.

Low dose, radiation dose <75.6 Gy; high-dose, radiation dose >75.6 Gy. Figures in parentheses are 95% confidence intervals.

While this study is a retrospective analysis, it gives some insight into outcomes of long-term leuporelin treatment added to external beam radiation, and in that context is of value despite the evidence level. Unfortunately, specific numbers that received leuporelin are unknown, and the dosage is unknown and likely variable.

Remaining efficacy studies are of a lower level of evidence and do not all use leuporelin in their protocol. They are tabulated as follows in terms of treatment and outcome, and points to note in terms of this submission.

Table 3: Efficacy studies

Study	Therapy	Comparator	Duration	Indication	Primary outcome	Of note
Heyman 2007 (n = 123)	Leuporelin in equiv. 7.5mg monthly for 9 months. Flutamide 750mg daily for 9 months. RT after androgen max 'response' (median 4.7mo)	N/A	5 years	Clinically localised prostate cancer	5 year biochemical DFS 63 ± 7%. Those initiating after 6 months of blockade had sig lower DFS.	About 50% had the category of disease of interest.
Solberg 2011	Subanalysis of Widmark 2009		Biopsy at 45 months follow-up. Assessed 3/12 for 1	Locally advanced prostate	Residual cancer in 66% (n=41) endocrine only patients and	Use of adjuvant ADT appears to have

Study	Therapy	Comparator	Duration	Indication	Primary outcome	Of note
			year then 6/12 until death or Feb 2008.	cancer.	22% (12) ADT+RT patients; p<0.0001.	significantly decreased rate of residual cancer in an appropriate population.
Stone 2000 (n=296)	Leuprorel in (dose unknown) 3 months before and after brachy implant. +flutamide 750mg daily 3 months before and after implant. + brachy implant.	N/A	2 years. Assessed every 6/12 and at 2 years after implant.	Prostate cancer (note not specific category)	30 (10%) had post implant biopsies. 4 were positive in who received hormone blockade, while 26 were positive in those who had not (p=0.002)	Again demonstrates the role of ADT in reducing post-treatment positive biopsy. Link to clinical outcomes. Only benefited high-risk in sub analysis.
Stone 1999 (n=145)	Leuprorel in (dose unknown) 3 months before and after brachy implant. +flutamide 750mg daily 3 months before and after implant. + brachy implant.	N/A	4 years. Assessed 3 and 6 months and 6 month intervals thereafter. Biopsy at 2 years.	Localised prostate cancer.	Prostate volume, freedom from PSA-defined failure. Mean PV reduction 35% (R2-62). 4-year actuarial freedom from PSA failure (PSA>1.0ng/mL) was 85%.	Demonstrates the reduction in prostate volume achieved. What proportion due to ADT or RT unknown.
Zelevsky 1997 (n=214)	Leuprorel in 7.5mg monthly from 3	N/A	-	Clinically localised	Size of prostatic tumours in relation to	Not all patients were high-risk

Study	Therapy	Comparator	Duration	Indication	Primary outcome	Of note
	months before RT until last day of RT treatment + Flutamide 750mg daily from 3/12 prior to last day + 3D conformational RT			prostate cancer	other structures. In the 45 patients prospectively evaluated, the median target-volume reduction after administration of NHT was 68 mL, representing a 27 % reduction in the size of the target volume. The 3 Year actuarial survival and disease-free survival rates were 93 %, and 83%, respectively.	classification.
Fransson 2009	Substudy of Widmark 2009	-	Assessed 3/12 for 1 year, then 6/12, then at years 1, 2, 4, 8 and 10.	Locally advanced prostate cancer	Moderate to severe urinary 'bother' 64 (18%) on ADT+RT vs 39 (12%) on ADT alone (p=0.005) QoL at 4 years similar apart from decreased social function in those receiving RT+ADT	QoL type endpoints were focussed upon in this substudy. Generally, there were more problems in those receiving RT.
Lund 2013	Substudy of Widmark 2009	-	5 years	Locally advanced prostate cancer	Generally higher symptom burdens in those receiving combination treatment.	Nil
Berg	Leuprorel	N/A	5 years	Locally	Evaluated	

Study	Therapy	Comparator	Duration	Indication	Primary outcome	Of note
2009 (n=86)	in 3.75mg equiv. monthly for 3 months. +flutamide 750mg daily until progression or death +3D conf. RT after 3/12 of ADT.			advanced prostate cancer	HRQoL and hormonal changes in those who'd used ADT for 5 years, adjuvant to RT. Compared with NORM, patients scored statistically ($p < 0.05$) and clinically (effect size ≥ 0.4) lower on sexual domains, and statistically ($p < 0.05$) lower on physical function and vitality. Estimated free testosterone and measured serum oestradiol had increased from baseline in most patients, but did not correlate with HRQoL outcomes 5 years after the start of treatment.	
Kohutek 2016 (n=2011)	EBRT, brachytherapy, or both + Leuprorel in 7.5mg monthly started 3-5 days before bicalutam	EBRT or brachytherapy or both.	At least 5 years assessed 3-6/12 for first 5 years, then annually.	T1-T3 prostate cancer	ADT at time of RT: significantly higher 10 year incidence of cardiovascular events (CE: 19.6%; 95% CI 17.0-22.6%) vs no ADT (CE: 14.3%; 95% CI 12.2-16.7%;	Although low level data, a large population studied. A long-term safety item to consider when using.

Study	Therapy	Comparator	Duration	Indication	Primary outcome	Of note
	ide 50mg daily for 30 days.				p=0.005)	
Pervez 2010	Leuprorel in 22.5mg every 3/12 up to 6/12 before RT and continuing for 2-3 years.	N/A	Up to 3 years.	Locally advanced prostate cancer	Maximum acute toxicity scores. 21(35%) had Grade 2 GI toxicity. 4 (6.67%) had Grade 3 genitourinary toxicity; 30 (33.33%) had Grade 2 GU toxicity.	

The best evidence presented showed a significant improvement in 5 year PFS with adjuvant ADT and RT vs ADT alone. This used leuprorelin for 3 years. However, this did not result in improved overall survival (Mottet 2012).

Cumulative PSCM (at 7 Years) was reported as 9.9 % (95% CI 7.1 to 12.8%) in the endocrine group and 6.3 % (95% CI 3.9 to 8.6%) in the endocrine + RT group (difference 3.7 %; 0.0 to 7.4 %). The relative risk of cancer-specific death was 0.44 (0.30–0.66, $p < 0.0001$) in favour of the endocrine plus radiotherapy treatment group (Widmark 2009). Use of leuprorelin and ADT in general has demonstrated reduced tumour volume and reduced likelihood of biopsy positive results (Solberg 2011; Stone 2000; Stone 1999; Zelefsky 1997). Ten-year OS was improved by the addition of ADT to RT treatment in high risk prostate cancer patients (Nguyen 2013).

Limitations of the data include the level of evidence of most of the submission, and the facts that: (1) leuprorelin was not exclusively used in most studies; (2) dosing was variable in duration, from near the time of radiation to considerably longer post-RT treatment; (3) classification of disease state varied across studies and only some subjects would be considered high risk localised prostate cancer in some of the publications, and; (4) treatment dosages in many of these studies is half that proposed in the PI. Pevez, Kohutek and Zelefsky used dosages recommended by the PI. Others were unknown.

Safety

The data submitted collectively measure exposure in 2,313 patients receiving doses of between 3.75 mg per month to 22.5 mg every 3 months for a period of 3 months to up to 18 years.

Mottet 2012 provides long term (3 year) data in 264 patients receiving leuprorelin, with only one month of concomitant flutamide at 750 mg daily. One must note the dosage was half that recommended in the PI. A trend toward higher mortality in the ADT + RT arm was noted with SAEs attributed to treatment also higher.

Widmark 2009 provides an experience in 875 patients, again at half dose, for 3 months treatment. Concomitant use and prolonged post-leuprorelin use of flutamide makes any attribution of AEs to leuprorelin difficult. Of note is that far more GU and GI toxicities occurred in the ADT alone group (250 versus 30) [see Attachment 2]. Significantly more patients in the endocrine + RT group had urinary incontinence, urgency, urethral stricture,

and erectile dysfunction. The difference in intestinal symptoms was not significant ($p = 0.075$).

While Kohutek 2016 was low level evidence of a retrospective analysis focussed upon cardiovascular events, there were $n=2011$ subjects studied and the 10-year incidence of post-RT CEs was significantly greater among patients receiving ADT at the time of RT (19.6%, 95 % CI: 17.0 % to 22.6 %) compared with patients treated with RT alone (14.3%, 95 % CI: 12.2 % to 16.7 %, $p = 0.005$). These results were not differentiated according to risk level of prostate cancer (T1 to T3). On multivariate analysis, both ADT at the time of RT ($p = 0.007$) and the time of salvage ($p = 0.0004$) were associated with increased CE risk, as were advanced age ($p = 0.02$), smoking ($p = 0.0007$), history of diabetes ($p = 0.0007$), and history of CE before RT ($p < .0001$).

Given the evidence level of the remaining data, this Delegate considers post-market experience more relevant in assessing any new ADRs or ADRs occurring at different rates for leuprorelin. The third PBRER encompassing 21 July 2014 to 20 July 2015 notes the following:

- The drug is approved in 87 countries for palliative treatment of prostate cancer.
- World-wide exposure to the drug in this period was approximately 1,922,337 patient-years.
- 31 SAEs were reported with a cumulative total of 1,189.
- QT prolongation associated with ADT was added to EU and US package inserts. A similar warning is present in the draft annotated PI at p18.
- No other information causing a change to the risk/benefit profile was identified.

Risk management plan

Not applicable.

Risk-benefit analysis

Delegate's considerations

The following clinical points frame the considerations of the Delegate for this submission:

- The best evidence presented, in the view of the Delegate, Mottet 2012 has the following issues:
 - The leuprorelin dose is half that intended for the PI.
 - Those with Gleason Score 8-10 were only 16.8% of the ADT group and 24.1% in the ADT+RT group, thus one must consider if the data may be considered to represent “high-risk, localised and locally advanced hormone-dependent prostate cancer”.
 - While PFS showed considerable advantage with combined therapy, (median follow-up of 67 months, 5-Year PFS Kaplan-Meier estimates were 60.9% for combined therapy vs. 8.5% with ADT alone (ASTRO; $p < 0.0001$), and 64.7% vs. 15.4%, respectively, for Phoenix ($p < 0.0011$)), OS was not statistically significantly different between groups.
- Widmark 2009 showed favourable cancer specific mortality in a treatment group receiving leuprorelin, (cumulative PSCM (at 7 Years) was reported as 9.9 % (95% CI 7.1 to 12.8%) in the endocrine group and 6.3 % (95% CI 3.9 - 8.6%) in the endocrine +

RT group (difference 3.7 %; 0.0 to 7.4 %)). However, dosage was again half that in the draft PI and lasted 3 months only, with flutamide the prolonged treatment. Given that flutamide binds the androgen receptor and prevents testosterone-stimulated prostatic DNA synthesis, as well as inhibiting prostatic nuclear uptake of androgen, this is a significant confounder in long-term results in this trial.

- The third study this Delegate considers worthy of singling out is that of Nguyen 2013 (n=741). Of these study subjects, 295 received ADT for over 2 years (R2-18 years) and consisted of either bilateral orchidectomy, or IM leuprorelin with or without bicalutamide. Median treatment for ADT was 2.9 years. No patient received less than 2 years of ADT. In addition, ALL patients were high risk, that is, \geq T3, Gleason score \geq 8, or PSA \geq 1.0 ng/mL. At 5 years, men who had not received ADT and had received radiation dose $<$ 75.6 Gy had higher clinical local failure rates than those given ADT and radiation dose $<$ 75.6 Gy (24.2% versus 0%, $p < 0.0001$). The points to note for these data are:
 - The data are retrospective.
 - Leuprorelin dose is unknown.
 - Actual numbers receiving leuprorelin are unknown.
- In considering safety, no new information beyond the QT prolongation raised by the PBRER is evident. The PI addresses this issue.

Summary of issues

The submission is literature based for clinical evidence. The submission consists of clinical data only. Key points in the view of the Delegate are as follows:

- The definition of high-risk, localised and locally advanced varies between the publications submitted and in the literature.
- The dosage in the principal studies of highest weight is half that recommended in the PI.
- Most of the evidence for the use of this product provided by the submission is based upon androgen blockade per se, not by this product specifically.
- Most of the studies have concomitant use of other blocking drugs, making quantification of effect by leuprorelin as well as circumscription of ADRs difficult.
- Duration and timing of treatment is inconsistent across studies and there is no clinically accepted regimen in the literature.
- The principal study using the specific drug, and for a prolonged period; (Mottet 2012, level II evidence) demonstrated a statistically significant benefit in PFS (primary endpoint at 5 years) but not in OS.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Eligard leuprorelin should be approved for registration.

Request for ACM advice

1. What is the Committee's view on the assumption of efficacy for leuprorelin being partly based upon the data for androgen blockade in general?
2. Is the Committee satisfied that the data are an adequate representation of "high-risk localised and locally advanced hormone-dependent prostate cancer"?

3. Is the Committee of the view that sufficient favourable data are presented to allow this extension of indication?

Response from sponsor

The submission is literature based for clinical evidence. The submission consists of clinical data only. This section will address the key points raised by the view of the Delegate.

Advice sought by the delegate

1. What is the Committee's view on the assumption of efficacy for leuprorelin being partly based upon data for androgen blockade in general?

Please refer to the information provided in response to Key Points 3 and 4 below.

2. Is the Committee satisfied that the data are an adequate representation of "high-risk localised and locally advanced hormone-dependent prostate cancer"?

Please refer to the information provided in response to Key Points 1, 3, 4 and 5 below.

3. Is the Committee of the view that sufficient data are presented to allow this extension of indication?

Please refer to the information provided in response to Key Points 1, 2, 3 and 5 below.

- ***Key Point 1: The definition of high-risk, localised and locally advanced varies between the publications submitted and in the literature.***

The definition of high-risk localised and locally advanced prostate cancer does vary between publications submitted and in the literature, as well as guidelines adopted by each country. The sponsor acknowledged this issue in the Clinical Summary and provided extensive comparative information on the pathology and surrogate measures such as PSA concentrations used to grade prostate cancers across various Guidelines, and to provide a consensual based summary to assist in categorising the individual publication populations submitted with this application. While there remains a degree of inconsistency in the cut off values of the parameters used to classify prostate cancer as high risk, there is agreement that histological grading, Gleason score and PSA plasma concentrations should be the measures utilised in any risk categorisation of prostate cancer. Furthermore, there is a high degree of consistency between the T and pT pathology grading systems, which assess both the degree of gland and external tissue involvement.

The table below summaries relevant local and international guidelines and collates parameters common to all guidelines into a broad definition which was used to screen the inclusion criteria used in the publications submitted with the application.

All studies submitted in this application, recruited patients who essentially met the criteria defining 'high risk' outlined in this overview.

Table 4: Classification system and high risk definition

Classification system	High risk definition (either of the below)
Australia (Duchesne publication)	<ul style="list-style-type: none"> • T3 histological grading of glandular components of prostate biopsy • Gleason score 8 to 10 • PSA > 20 ng/mL
New Zealand (Ministry of Health guideline)	<ul style="list-style-type: none"> • T > 3 or 2 • Gleason score > 8 • PSA > 20 ng/mL • T2b or Gleason 7 or PSA 10-20 ng/mL
USA (National Comprehensive cancer Network practice guidelines)	<ul style="list-style-type: none"> • T3a • Gleason score 8-10 • PSA > 20ng/mL
Module 2.5 Clinical Overview High-risk, localised and locally advanced prostate cancer	<ul style="list-style-type: none"> • T2 or T3a - Primary tumour within or just beyond the prostate gland • Gleason score ≥ 8 • PSA ≥ 20 ng/mL

For example the pivotal study by Mottet 2012 included patients if they had histologically confirmed, locally advanced (T3-4 N0), or pathologic (p)T3 prostate adenocarcinoma without documented nodes or metastases. Similarly the pivotal study by Widmark 2009 included patients categorised as clinical T1b-T2, G2-G3 (grading system unrelated to Gleason, grading malignant cell differentiation), or T3 (TNM-classification 1992), any WHO Grade 1-3; prostate specific antigen (PSA) of 70 ng/mL or less; and no evidence of metastases as determined by bone scanning and pulmonary radiography.

Examples of supportive studies include Stone 2000, Nguyen 2013 and Zelefsky 1997. They enrolled patients if they had a Gleason score ≤ 6, stage T1c - T2b and PSA ≤ 20 ng/mL, if they were categorised as high-risk prostate cancer (clinical classification ≥ T3, Gleason score ≥ 8, or prostate-specific antigen level ≥ 20 ng/mL), or as high-risk patients if they presented with T2c or T3 tumours or Gleason scores of 8 and above, respectively.

The PI does not specify the criteria for high-risk, localised or locally advanced prostate cancer due to the different criteria used globally and in the literature. Due to this variability, no criteria for the definition has been included in the proposed PI. Hence as the PI stands, this would be the judgement of prescribers based upon the clinical literature and the current relevant guidelines for prostate cancer.

• ***Key Point 2: The dosage in the principal studies of highest weight is half that recommended in the PI***

The dosage used in the principal studies of highest weight did use half the recommended dose as recommended in the PI and this information has been communicated in the PI. The PI now includes information that clearly states that some of the pivotal studies employed half of the currently recommended dose of leuprorelin.

These same principal studies were also submitted in Europe and no changes to the posology was required in the SmPC for the use as neoadjuvant or adjuvant therapy in combination with radiotherapy in high-risk localised and locally advanced prostate cancer.

These studies (Mottet 2012 and Widmark 2009) were designed to investigate the impact of radiotherapy on androgen deprivation therapy (ADT) and not the impact of leuprorelinbased ADT on radiotherapy. The reduced dosage used in these pivotal studies is unlikely to negatively impact on the efficacy outcomes observed, however the safety profile reported may underestimate the market incidence. As concluded in the latest PSUR, the overall adverse event profile of Eligard has been well established in both clinical studies and post approval marketing experience. From this review, it has been concluded that the safety data remains in accord with the previous cumulative experience and with

the Reference Safety Information. Based on the conclusion in the PSUR, the additional indications approved in Europe in 2014 did not significantly affect the safety profile of the product.

Furthermore, the supportive efficacy studies by Heymann 2007 and Zelefsky 1997 used the standard dose of leuprorelin, while Nguyen 2013 and Stone 2000 administered leuprorelin according to the existing standards of care current at the time of the studies. The safety studies by Berg 2009, Kohutek 2016 and Pervez 2010 all used the standard leuprorelin doses.

The percentage of patients recording five-year outcomes in Heymann were biochemical disease-free survival, (DFS) $63\% \pm 7\%$; clinical DFS, $75\% \pm 5\%$; cancer-specific survival, $99\% \pm 1\%$; and overall survival, $89\% \pm 3\%$. Zelefsky found that neoadjuvant ADT reduced the volume of normal rectal, bladder and small bowel tissue exposed to radiation by 18, 46 and 91% respectively.

Nguyen found that biochemical disease free survival rates increased from 73.9% in patients receiving high dose radiation only to 82% in patients receiving high dose plus ADT. Stone demonstrated that post treatment positive biopsies in patients receiving ADT were seen in 3.5% compared to 14% who did not.

- **Key Point 3: Most of the evidence for the use of this product provided by the submission is based upon androgen blockage per se, not by this product specifically.**

Leuprorelin was not exclusively used in most studies as bridging data from LHRH analogues was also used to support this application. LHRH-analogues mainly exert their effects through receptor de-sensitization in the anterior pituitary gland. As a consequence, plasma testosterone is diminished to castration level. According to scientific literature, desired and undesired effects of LHRH analogues used in prostate cancer are a consequence of their pharmacodynamics action in lowering testosterone, as a class effect. Thus, due to the same desired low testosterone level effects, data from other LHRH-analogues is regarded as an acceptable substitution for leuprorelin.

This conclusion is supported by advice in both the US NCCN guidelines and Australian Cancer Network Clinical Practice Guidelines 2010 (ACN) which make no specific recommendation regarding the most appropriate agents to be used in an ADT treatment regimen. The ACN provide the following advice regarding the choice of ADT: A recommendation cannot be made on the basis of the current evidence.

It should be noted that 3 of the 13 studies submitted in this application administered leuprorelin only (Pervez 2010) or leuprorelin in combination with flutamide 750mg daily for only a short period of the total treatment period (Mottet 2012 and Kohutek 2016). Pervez and Kohutek were safety studies and are discussed under point 4. Mottet 2012 administered leuprorelin for 3 years, with flutamide added to the regimen only in the first month of treatment. In the radiotherapy arm, the median duration of treatment was 55 days (range: 48 to 85). The median duration for hormone therapy for the ADT group was 2.5 years (range: 0.3 to 3.6) and 3.0 years (range 0.3 to 3.5) for the combined group. 60.9% of patients in the combined arm were censored for PFS at 5 years (primary endpoint) compared with 8.5% with ADT alone ($p < 0.0001$). Mottet concluded that the addition of RT to 3 years of ADT significantly reduces the risk of progression and improves locoregional control and metastasis-free survival in patients with locally advanced prostate cancer.

- **Key Point 4: Most of the studies have concomitant use of other blocking drugs, making quantification of effect by leuporelin as well as circumscription of ADRs difficult.**

As discussed in our response to Key Point 3, bridging data from other LHRH-analogues is regarded as an acceptable substitution due to same desired and undesired effects of plasma testosterone suppression. Expected pharmacological consequences of testosterone suppression is also included in the Adverse Effects section of the Eligard PI. These adverse effects are not specific for leuporelin but can also encompass the other androgen blocking drugs.

As the circumscription of ADRs is difficult due to the use of other blocking drugs, the PI does not include the frequencies of the adverse effects when used in combination with radiotherapy. However a statement has been included to communicate the increased toxicities of the combined use of leuporelin acetate with radiotherapy.

We also wish to point out that some of the studies were designed to evaluate the impact of radiotherapy on ADT and not the impact of ADT on radiotherapy. Thus the use of concomitant drugs shall not affect the impact of radiotherapy on ADT and consequently can be used as adequate supporting data in this application.

The safety studies by Pervez and Kohutek administered leuporelin only (Pervez 2010), or leuporelin in combination with an anti-androgen for only a short period of the total treatment period. Kohutek 2016 administered leuporelin for a median of 6.1 months (range: 0.9 to 149 months), while bicalutamide 50mg daily was administered for only 30 days. The outcomes observed in these studies could therefore be reasonably proscribed to leuporelin alone or in combination with radiotherapy.

In Pervez, leuprolide acetate 22.5 mg, administered subcutaneously every 3 months was prescribed for up to 6 months neoadjuvantly, followed by concurrent hormonal therapy during RT and continuing after RT for 2 to 3 years. The maximum acute toxicity scores after radiation were 21 (35%) patients with Grade 2 gastrointestinal (GI) toxicity; 4 (6.67%) patients with Grade 3 genitourinary (GU) toxicity; and 30 (33.33%) patients with Grade 2 GU toxicity. These toxicity scores were reduced after RT but whilst receiving leuporelin; there were only 8 (13.6%) patients with Grade 1 GI toxicity, 11 (18.97%) with Grade 1 GU toxicity, and 5 (8.62%) with Grade 2 GU toxicity at 3 months follow up.

While Kohutek showed that patients receiving ADT at the time of RT exhibited significantly higher 10-year incidence of cardiovascular events (CE) (19.6%, 95% CI 17.0% to 22.6%) than those not receiving ADT (14.3%, 95% CI 12.2% to 16.7%, $p = 0.005$), other parameters were also strongly associated in CE. As well as ADT at the time of RT ($p = .007$) and the time of salvage ($p = 0.0004$), advanced age ($p = 0.02$), smoking ($p = 0.0007$), history of diabetes ($p = 0.0007$), and history of CE before RT ($p < 0.0001$) were associated with increased CE risk.

- **Key Point 5: Duration and timing of treatment is inconsistent across studies and there is no clinically accepted regimen in the literature.**

This application was supported by a LBS. The process applied to identifying and selecting all studies relevant to the objectives of the application are designed to minimise the potential impact of study selection bias, so an objective decision on the safety and efficacy of leuporelin in the proposed indication can be made. The process must be agreement with TGA.

While the quality of the evidence is evaluated in the Clinical Summary, all evidence relevant to the decision is provided, regardless of design limitations. Therefore clinical data from 13 published studies relevant to the use of combination radiotherapy and ADT therapy, and specifically data on short-term versus long-term ADT in combination with radiotherapy have been submitted in support of this application.

International treatment guidelines recommend the use of radiotherapy and ADT in both high-risk localised and locally advanced prostate cancer. A summary of the different treatment recommendations is provided below.

Table 5: Treatment recommendations across territories

Source	Recommendation
Australia (Duchesne publication)	The optimal duration of treatment is still under investigation but is likely to be between 6 months and several years, depending on the risk grouping.
USA (National Comprehensive cancer Network practice guidelines)	Patients with high-risk and very high-risk cancers should receive neoadjuvant/concomitant/adjuvant ADT for a total of 2 to 3 years if comorbidities allow.
New Zealand (Ministry of Health guideline)	In high risk patients, long-term ADT prior to, during and after External Beam Radiation Therapy (EBRT) is recommended as it increases overall survival. EBRT should start five months after beginning ADT. Optimal duration for ADT is uncertain but can be considered for up to three years if tolerated well.
Europe (European Association of Urology guideline)	In daily practice, ADT starts either at the onset of radiotherapy (for adjuvant ADT) or two or three months before (for neoadjuvant), but the concomitant component is crucial to potentiate radiotherapy. Long-term ADT, ranging from two to three years is recommended for locally advanced disease, rather than short term (six months).

We acknowledge there is no clinically accepted regimen for the duration and timing of treatment. This has been reflected in the PI as no information on the duration or timing of treatment is provided for the combination therapy and instead would be left to the judgement of prescribers based upon the clinical literature.

Due to the inconsistent treatment regimens submitted in support of this application, the PI includes the following statement to address the limited data:

Long term safety data on the combination therapy was limited due to long term use of an anti-androgen in some studies, but limited use of leuprorelin.

The use of this combination therapy is widely endorsed in the international guidelines, however it is still considered off-labelled use as it is not currently registered in the indication. The PSUR includes a number of off-label use adverse events due to the use of Eligard in association with radiotherapy. Due to the clear benefits of the proposed combination therapy, which is already adopted in current clinical practise, we believe that the proposal to extend the indications of leuprorelin is adequately supported by the evidence provided in this submission.

- **Key Point 6: The principal study using the specific drug, and for a prolonged period; (Mottet 2012, level II evidence) demonstrated a statistically significant benefit in Progression Free Survival (PFS) (primary endpoint at 5 years) but not in Overall Survival (OS).**

The difference in the primary end point, 5 year PFS was highly significant. 60.9% of patients in the combined arm recorded PFS at 5 years compared with 8.5% with ADT alone ($p < 0.0001$). While the benefits in PFS with combined therapy in the current study did not translate into a survival advantage at 5 years, the authors noted that median overall survival had not been reached in either treatment arm at the time of analysis (67month follow-up), with Kaplan-Meier estimates of mortality around 71% in both treatment arms. Nine patients receiving combination therapy and 18 receiving ADT alone died due to their prostate cancer, giving survival incidences of 93.2% versus 86.2% ($p = 0.0586$).

A number of factors could have contributed to the results, including the relatively small population and a relatively short follow-up period. The radiotherapy regimen implemented could be considered outdated based on current treatment practices and

might not reflect more specific therapeutic approaches. The authors concluded that a longer follow-up is needed to assess the potential survival impact.

The use of radiotherapy to treat the 24 patients progressing after ADT alone may have had an impact on the survival outcome. Metastases and locoregional recurrence may have been under-estimated due to the absence of systemic imaging evaluations at predefined time points.

As mentioned previously in response to Key Point 2, this study was designed to investigate the impact of radiotherapy on ADT and not the impact of leuprorelin-based ADT on radiotherapy. Statistically significant benefit was achieved for the primary objective (PFS), as well as other secondary objectives (locoregional control and metastasis-free survival), however no statistically significant benefit was achieved for OS, which was a secondary objective.

Advisory Committee Considerations¹¹

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Eligard modified release injection syringes containing 7.5 mg, 22.5 mg, 30 mg and 45 mg of leuprorelin to have an overall positive benefit-risk profile for the indication:

Current:

Palliative treatment of advanced prostate cancer

Proposed: The addition of:

Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

In making this recommendation, the ACM:

- noted inconsistencies in definition of high risk, localised and locally advanced between publication submitted and literature
- dosage weight discrepancy in principal studies
- data is based on androgen blockade
- most studies include concomitant use of other drugs
- duration and timing of treatment is inconsistent across studies
- principal study using specific medicine did not demonstrate a statistically significant improved overall survival rate using leuprorelin versus radiation therapy alone.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

¹¹ The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA
- Negotiation of the PI and CMI to the satisfaction of the TGA

Proposed PI/CMI amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI).

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

- *1. What is the Committee's view on the assumption of efficacy for leuprorelin being partly based upon the data for androgen blockade in general?*

The ACM agreed that the data provided partly based on androgen blockade is acceptable with general castration data being extrapolated from the data.

- *2. Is the Committee satisfied that the data are an adequate representation of "high-risk localised and locally advanced hormone-dependent prostate cancer"?*

The ACM agreed that the data are an adequate representation of 'high-risk localised and locally advanced hormone-dependent prostate cancer'. ACM noted that the data relates to this wording even though it leaves some of the patient selection criteria to the clinician.

- *3. Is the Committee of the view that sufficient data are presented to allow this extension of indication?*

The ACM were of the view that sufficient data was presented to allow the proposed extension of indication. The ACM noted that the CMI is adequate for standard format but not particularly informative such as information on sexual dysfunction. The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Eligard (leuprorelin acetate) (7.5 mg, 22.5 mg, 30 mg, 45 mg) modified release injection syringe.

The **new** indications are:

Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy

The **full** indications are:

§ *Palliative treatment of advanced prostate cancer*

§ *Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy*

Attachment 1. Product Information

The PI for Eligard approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>