

**PROSTAP[®] SR DCS 3.75mg Powder and Solvent for
Prolonged-release Suspension for Injection in Pre-filled Syringe**

(leuprorelin acetate)

PL 16189/0012

UKPAR

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LAY SUMMARY

This is a summary of the public assessment report (PAR) for PROSTAP[®] SR DCS 3.75 mg Powder and Solvent for Prolonged-release Suspension for Injection in Pre-filled Syringe. This medicinal product will be referred to as PROSTAP[®] SR DCS in the remainder of this report.

This summary explains how PROSTAP[®] SR DCS was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use PROSTAP[®] SR DCS.

For practical information about PROSTAP[®] SR DCS, patients should read the package leaflet or contact their doctor or pharmacist.

What is PROSTAP[®] SR DCS and what is it used for?

PROSTAP[®] SR DCS is a synthetic hormone and contains the active substance leuprorelin acetate, which can be used to reduce the levels of testosterone and estrogen circulating in the body.

PROSTAP[®] SR DCS is identical to a currently authorised product (line extension), Prostap[®] SR 3.75 mg prolonged release powder for suspension for injection (PL 16189/0008), except for the presentation of the products.

PROSTAP[®] SR DCS is used to treat prostate cancer in men and endometriosis and uterine fibroids in women. It can also be used to reduce the thickness of the lining (endometrium) of the womb (uterus) in preparation for surgery.

How is PROSTAP[®] SR DCS used?

PROSTAP[®] SR DCS is given in the arm, thigh or abdomen once a month. The injection site should be varied at regular intervals. If patients are going to be given PROSTAP[®] SR DCS prior to intrauterine surgery a single injection 5-6 weeks before surgery is received. Patients with endometriosis will be given an injection of PROSTAP[®] SR DCS for a period of 6 months only and treatment will be initiated during the first five days of the menstrual cycle. Patients with uterine fibroids will receive an injection of PROSTAP[®] SR DCS once a month usually for 3-4 months before surgery.

This medicine is only available on prescription from a doctor.

For further information on how PROSTAP[®] SR DCS is used, please see the Summary of Product Characteristics available on the MHRA website.

How does PROSTAP[®] SR DCS work?

PROSTAP[®] SR DCS is a nonapeptide analogue of the natural female hormone Gonadotropin Releasing Hormone (GnRH). It works by reducing the levels of testosterone and estrogen circulating in the body and also reduces the thickness of the lining of the womb in preparation for surgery.

How has PROSTAP[®] SR DCS been studied?

No new data has been submitted as this is a line extension application of the currently authorised PROSTAP[®] SR 3.75 mg prolonged release powder for suspension for injection (PL 16189/0008). The only difference relates to the presentation of the products.

What are the benefits and risks of PROSTAP[®] SR DCS?

Because PROSTAP[®] SR DCS is a line extension application, it is considered to be therapeutically equivalent, to Prostag[®] SR 3.75 mg prolonged release powder for suspension for injection (PL 16189/0008). Therefore, its benefits and risks are taken as being the same as those of Prostag[®] SR 3.75 mg prolonged release powder for suspension for injection (PL 16189/0008).

Why is PROSTAP[®] SR DCS approved?

No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of taking PROSTAP[®] SR DCS outweigh the risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of PROSTAP[®] SR DCS?

A risk management plan has been developed to ensure that PROSTAP[®] SR DCS is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for PROSTAP[®] SR DCS, including the appropriate precautions to be followed by healthcare professionals and patients. Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored continuously as well.

Other information about PROSTAP[®] SR DCS

A Marketing Authorisation was granted on 28th April 2011.

For more information about treatment with PROSTAP[®] SR DCS, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2014.

The full PAR for PROSTAP[®] SR DCS follows this summary.

**PROSTAP® SR DCS 3.75 mg Powder and Solvent for
Prolonged-release Suspension for Injection in Pre-filled Syringe**

PL 16189/0012

SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product PROSTAP[®] SR DCS 3.75 mg Powder and Solvent for Prolonged-release Suspension for Injection in Pre-filled Syringe (PL 16189/0012) to Takeda UK Limited on the 28th April 2011. This product will be referred to as PROSTAP[®] SR DCS throughout this report.

This is a prescription-only medicine (POM) used to treat:

- (i) Metastatic prostate cancer.
- (ii) Locally advanced prostate cancer, as an alternative to surgical castration.
- (iii) As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.
- (iv) As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.
- (v) Management of endometriosis, including pain relief and reduction of endometriotic lesions.
- (vi) Endometrial preparation prior to intrauterine surgical procedures including endometrial ablation or resection.
- (vii) Preoperative management of uterine fibroids to reduce their size and associated bleeding.

PROSTAP SR DCS (Dual Chamber pre-filled Syringe) contains leuprorelin acetate, a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH) which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotropin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible on discontinuation of therapy.

This national application is a line extension application, under Article 8(3) of Directive 2001/83/EC, as amended; of the current authorisation (Prostap[®] SR 3.75 mg prolonged release powder for suspension for injection, PL 16189/0008). For the new application, the same prolonged release powder and the same diluent are presented in a dual chamber prefilled syringe (DCS) instead of being presented separately. The formulations of both the prolonged release powder and the diluent in the DCS are the same as for the current approved product. The methods of manufacture, specifications and testing methods of the powder and diluent do not change except for the differences due to the filling of the two product components in to the DCS. There are no changes in the proposed indications or route of administration.

Pharmacovigilance System and Risk Management Plan

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A satisfactory risk management plan has been provided for this product.

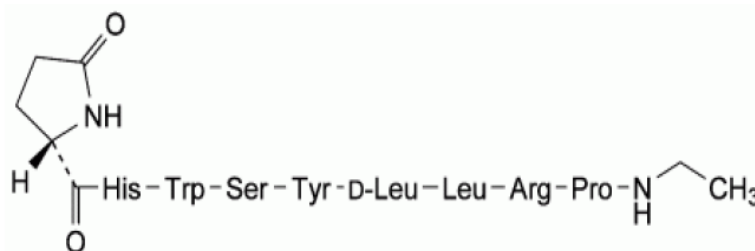
II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: Leuprorelin acetate

Chemical Name: 5-Oxo-1-prolyl-1-histidyl-1-tryptophyl-1-seryl-1-tyrosyl-d-leucyl-1-arginyl-N-ethyl-1-prolinamide

Chemical Structure:



Molecular Formula: C₅₉H₈₄N₁₆O₁₂

Molecular Weight: 1209

Physical form: White to almost white crystalline powder. Practically insoluble in water, freely soluble in methanol and in methylene dichloride.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) certificate of suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely gelatin, copoly (DL lactic acid/glycolic acid) 72:25 mol% and mannitol (E421) making up PROSTAP® SR DCS Powder. The sterile solvent is consisted of carmellose sodium, mannitol (E421), polysorbate 80, glacial acetic acid and water for injections.

All excipients are controlled to their respective European Pharmacopoeia specifications with the exception of copoly (DL lactic acid/glycolic acid) which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development

The objective of the pharmaceutical development programme was to present the prolonged release powder and diluent in a dual chamber prefilled syringe (DCS) instead of being presented separately to facilitate ease of use and product handling for the professional end-user with no effect on therapeutic activity.

The formulations of both the microsphere powder containing the leuprorelin and the sterile vehicle are identical to those of the currently approved Prostag SR product. The only difference is the presentation of these two components in the dual chamber syringe. No formulation development work was therefore carried out for this presentation.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

One dual chamber pre-filled syringe containing 3.75 mg leuprorelin acetate powder in the front chamber and 1 ml of Sterile Solvent in the rear chamber.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with guidelines concerning materials in contact with parenteral products.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for unopened pre-filled syringe has been set, with storage conditions of “Do not store above 25°C”, “Do not refrigerate or freeze” and “Store in the original container in order to protect from light”.

Once reconstituted with sterile solvent, the suspension should be administered immediately.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are pharmaceutically satisfactory.

Marketing Authorisation Application Form (MAA)

The MAA form is satisfactory.

Expert Report

The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There is no objection to the approval of this product from a pharmaceutical point of view.

III. NON-CLINICAL ASPECTS

This application was submitted as a line extension of a known active substance according to Article 8.3 of Directive 2001/83/EC, as amended. The use of leuprorelin acetate is well-established in the UK. The pharmacodynamic, pharmacokinetic and toxicological properties of leuprorelin acetate are well-known.

The applicant has not provided any new non-clinical data as the formulations and route of administration of both the leuprorelin acetate microsphere powder and the sterile solvent are identical to those used for the currently approved of Prostav SR product.

A non-clinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submitting the environmental risk assessment.

There is no objection to the approval of this product from a non-clinical viewpoint.

IV CLINICAL ASPECTS

Clinical Background

This is a line extension application for leuprorelin acetate 3.75 mg injection submitted under Article 8(3) of Directive 2001/83/EC, as amended, a 'known active substance'. The applicant already holds a national Marketing Authorisation for Prostav SR Leuprorelin Acetate Depot Injection 3.75 mg (PL 16189/0008). The use of these products is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, leuprorelin acetate.

Leuprorelin acetate is a synthetic analogue of the naturally occurring Gonadotropin Releasing Hormone (GnRH) first synthesized in 1974. The peptide has a longer half-life due to its increased resistance to peptidase degradation and is about 50 – 80 times more potent than the natural luteinizing hormone releasing hormone (LHRH) due to its enhanced binding affinity to the LHRH receptor. Worldwide, leuprorelin acetate is the most widely prescribed depot LHRH agonist, having been used in the treatment of prostate cancer for over twenty years.

In the UK and Ireland, the one-month (Prostav SR) formulation of leuprorelin acetate has been authorised nationally since 1990 for use in the treatment of prostate cancer and sex hormone dependent gynaecological conditions.

The currently authorised Prostav SR product is presented in glass vials containing 44.1 mg of leuprorelin acetate microsphere powder (3.75 mg leuprorelin acetate) and glass, prefilled syringes containing 1 ml sterile solvent. The new presentation, which is the subject of this application, is a dual chamber pre-filled syringe (DCS) containing 44.1 mg Prostav SR powder (3.75 mg leuprorelin acetate) in the front chamber and 1 ml of sterile solvent in the rear chamber. The formulations of both the leuprorelin acetate microsphere powder and the sterile solvent are identical to those of the existing Prostav SR.

The applicant states that there is no difference in terms of the product formulations between the authorised Prostav SR and the proposed Prostav SR DCS. The only difference relates to the presentation of the products. Instead of a prefilled syringe containing the sterile vehicle and a separate Prostav powder vial, both products will be housed in separate chambers of a single prefilled syringe. This will further facilitate ease of use and product handling for the professional end-user with no effect on therapeutic activity. The route of administration, indications and dosage are also identical to those for the existing Prostav SR product.

The one-month DCS presentation is authorised in 21 countries worldwide and has been marketed in the EU since 1995. The applicant states that the existing body of clinical information is sufficient to characterise efficacy and safety. It is considered that the administration of Prostav SR DCS via a dual chamber pre-filled syringe system will not present any new safety issues.

Clinical pharmacology

No additional clinical studies are required, as there has been no change to the formulation, indications, dosage or route of administration. The existing clinical

information is sufficient to characterise the safety and efficacy of the proposed product, Prostap SR DCS.

Pharmacodynamics

No new data is required and none is submitted for this application.

Clinical efficacy

No new data is required and none is submitted for this application.

Clinical safety

No new data is required and none is submitted for this application.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC, PIL and labelling are satisfactory and consistent with the original Prostap SR product.

Marketing Authorisation Application (MAA) Form

The MAA form is satisfactory.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Clinical Conclusion

There are no objections to the approval of this product from a clinical point of view.

V. USER CONSULTATION

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for PROSTAP SR Leuprorelin Acetate Depot Injection 3.75 mg as the parent PIL. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of PROSTAP[®] SR DCS are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted as the formulations and route of administration of both the leuprorelin acetate microsphere powder and the sterile solvent are identical to those used for the currently approved of Prostav^{*} SR product.

EFFICACY

No new safety or efficacy data are submitted for this application. Leuprorelin acetate has a well-established side-effect profile and is generally well-tolerated.

The SmPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with leuprorelin acetate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the Marketing Authorisation application on 31 st July 2009
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 8 th August 2009
3	Following assessment of the application the MHRA requested further information on the quality section on the 17 th December 2009 and 25 th October 2010 and for the clinical section on the 4 th January 2010, 19 th November 2010 and 21 st March 2011
4	The applicant responded to the MHRA's requests, providing further information on the quality section on the 16 th September 2010 and 1 st February 2011 and on the clinical section on the 16 th September 2010, 1 st February 2011 and 6 th April 2011
5	The application was determined on 28 th April 2011

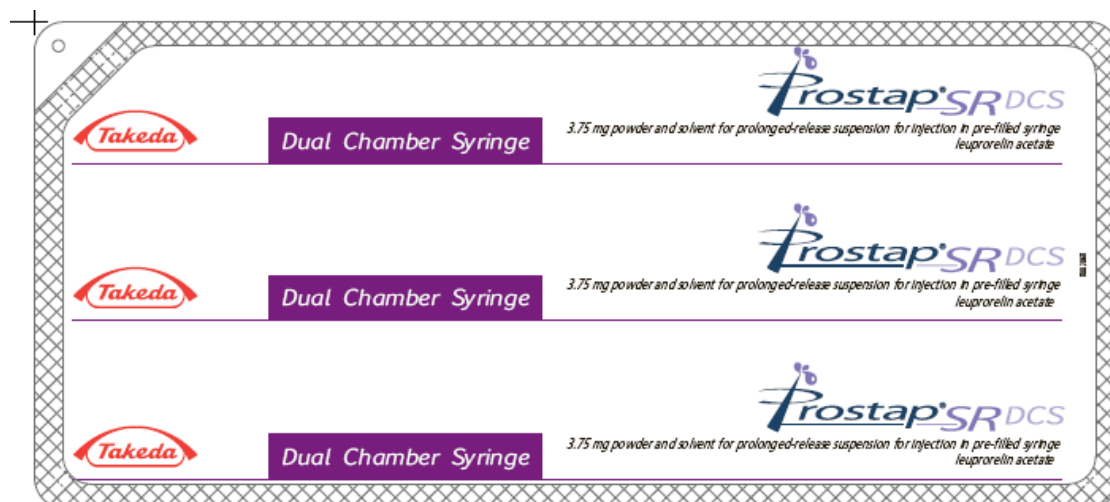
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING



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STEPS TAKEN AFTER ASSESSMENT

The following table lists some non-safety updates to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Description	Outcome
20/12/2013	VAR Medical Type II	To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC in line with the Company Core Data sheet and to include the indication 'Neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer'. In addition, to update the SmPC in line with the QRD template.	Variation granted 24/05/2014
30/04/2015	Medical Type II (standard)	To update section 4.2 (posology and administration) of the SmPC to reflect the recent developments in the treatment of castrate-resistant prostate cancer (CRPC) and current medical practice. As a consequence, the Health Professional Leaflet has been updated.	Variation granted 12/06/2015

ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT

Reason:

To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC in line with the Company Core Data sheet and to include the indication ‘Neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer. In addition, to update the SmPC in line with Quality Review of document (QRD) template.

Two other LHRH agonists, goserelin and triptorelin, are authorised for use as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

The Marketing Authorisation Holder (MAH) also proposes the following text for inclusion in section 5.1 of the SmPC:

Neo-adjuvant leuprorelin acetate prior to radiotherapy has been shown to significantly reduce prostate volume.

The MAH is also seeking to vary sections 2, 4.2, 4.3, 4.4, 4.6, 4.8 and 6.6 of the SmPC. These changes are not directly related to the proposed new indication.

Assessor’s comment:

Definition of high-risk localised and locally advanced prostate cancer

NICE Clinical Guideline CG58 (2008): *Prostate cancer diagnosis and treatment*, provides a definition of the terminology used in the proposed new indication:

Localised prostate cancer

Cancer which has been staged as T1 or T2 (confined to the prostate gland).

- Low-risk - PSA < 10 ng/ml and Gleason score ≤ 6 and clinical stage T1-T2a
- Intermediate-risk - PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b or T2c
- High-risk - PSA > 20 ng/ml, or Gleason score 8-10

The guideline states that high risk localised patients may also be considered under the heading of locally advanced disease.

Locally advanced prostate cancer

Cancer which has been staged as T3 or T4 (spread outside the prostate gland).

However, extra-pelvic lymph nodes, or organs distant to the pelvis, are not involved.

Staging terminology

Older studies use the Jewett staging system (A,B,C,D) rather than TNM:

B1 = T2a Confined to prostate and ≤ 1.5 cm

B2 = T2b/T2c Nodule > 1.5 cm, or >1 localised nodule

C1 = T3a Tumour extended beyond prostate with minimal extension

C2 = T3b/T3c Extension bilaterally and/or to seminal vesicles

Supporting Evidence

The MAH has not submitted new clinical data to support the proposed new indication. Instead, bibliographic evidence is submitted. The evidence is grouped into 4 main areas:

- Clinical pharmacology
- Clinical efficacy: prostate volume reduction
- Clinical efficacy: longer term outcomes
- Clinical safety

Assessor's comment:

The MAH has provided a summary of the literature search strategy used. This was acceptable to identify all relevant published studies to support the proposed indication.

Clinical pharmacology

The MAH has provided a discussion of the pharmacological basis and mechanism of action for the use of leuprorelin in the neo-adjuvant setting. Prostate cancer cells express androgen receptors. Continuous administration of LHRH analogues results in decreased levels of Follicle-Stimulating Hormone (FSH) and luteinizing hormone (LH), and a consequent reduction in testosterone to castrate levels. Suppression of testosterone is the principal mechanism by which LHRH agonists exert their effects in androgen sensitive tumours. Androgen deprivation therapy used prior to radiotherapy or prostatectomy has been shown to reduce prostate volume and serum prostate specific antigen (PSA). Histological changes include reduced proliferation and apoptosis of prostate cancer cells, and degeneration of prostatic vasculature.

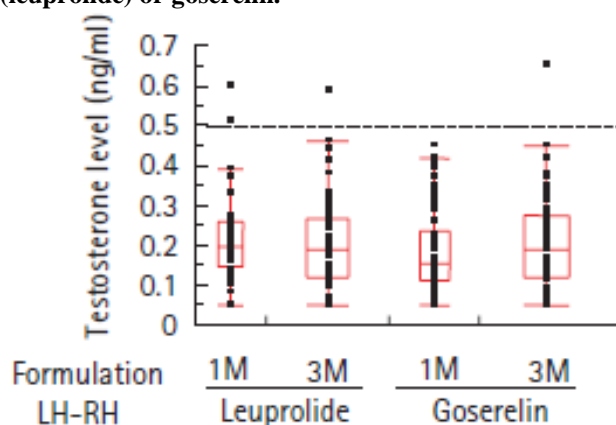
The MAH has submitted a published study which compares testosterone suppression by leuprorelin 3.75 mg/month (11.25 mg every 3 months) and goserelin 3.6 mg/month (10.8 mg every 3 months):

Fujii et al 2008

The aim of this retrospective study in Japanese prostate cancer patients was to compare the effects of goserelin and leuprorelin in the suppression of testosterone. 232 patients treated with luteinising hormone-releasing hormone agonist (LHRHa) from 1997 to 2006, from the database of the Cancer Institute Hospital, Tokyo, with pre- and post-treatment serum testosterone measurements, were enrolled. 70 patients (30%) had treatment for metastatic disease and the remainder had neo-adjuvant treatment prior to RT or prostatectomy, or when these treatments failed. The LHRHa used were leuprorelin 3.75 mg/month (or 11.25 mg every 3 months) and goserelin 3.6 mg/month (or 10.8 mg every 3 months). Castrate level was defined as ≤ 0.5 ng/ml. The assay was standardised.

Leuprorelin was taken by 108 patients and goserelin by 124. Mean baseline testosterone was similar between treatment groups. Testosterone levels were assessed a mean of 5.4 times during treatment. The mean maximum testosterone levels during 1-monthly leuprorelin, 3-monthly leuprorelin, 1-monthly goserelin and 3-monthly goserelin were 0.22, 0.20, 0.19, and 0.20 ng/mL respectively ($p=0.659$). Four patients (3 on leuprorelin, one on goserelin) had some measurements above castrate levels during treatment.

Figure 1: The maximum testosterone levels during treatment with 1- or 3-monthly leuprorelin (leuprolide) or goserelin.



Assessor's comment

This retrospective study provides evidence that leuprorelin 3.75 mg monthly or 11.25 mg 3-monthly can provide testosterone suppression to castrate levels in over 97% of patients. Maximum testosterone levels were comparable to goserelin.

The MAH has submitted 3 published studies which compare pharmacodynamics endpoints for leuprorelin at the 3.75 mg and 7.5 mg monthly doses:

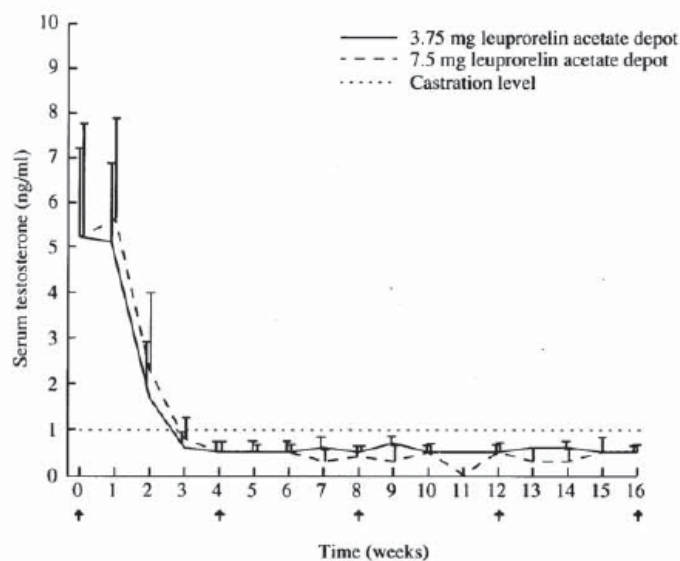
Bischoff 1990

Of 190 patients with prostate cancer (mean age 72) of any stage, 157 (82.8%) were treated with 3.75 mg leuprorelin subcutaneously once monthly, and 33 (17.2%) were treated with 7.5 mg leuprorelin subcutaneously or intramuscularly once monthly, for up to 15 months. Some patients also received anti-androgens. After 1 month of treatment, plasma testosterone, dihydrotestosterone, LH and FSH levels were suppressed. The author concludes no difference in effects between doses following analysis of the data. However this data is not provided in the report.

Akaza et al 1990

101 patients with T2-T4 prostate cancer were randomised 1:1 to receive 3.75 mg and 7.5 mg leuprorelin monthly by subcutaneous injection. The rate and extent of reduction of testosterone to castrate level (defined as 1 ng/mL) was comparable between groups:

Figure 2: serum testosterone concentrations in patients treated with 3.75 mg or 7.5 mg leuprorelin once every 4 weeks



Rizzo et al 1990

In this open-label study of locally advanced and metastatic prostate cancer, patients were randomised to receive monthly leuporelin injections until disease progression: 3.75 mg (n=30), 7.5 mg (n=8), 15 mg (n=8) and 30 mg (n=1). Following treatment, testosterone levels fell to castrate levels after 3 weeks and were maintained for the duration of treatment. The authors comment that no substantial differences were noted for different drug doses.

Mazzei et al 1989

In a dose response study, 22 patients with advanced prostate cancer were randomised to receive monthly leuporelin subcutaneous injection at doses of 3.75 mg, 7.5 mg, 15 mg or 30 mg until disease progression. Testosterone levels were reduced to castrate levels within the third week and maintained for the treatment duration. No significant differences in the levels of testosterone were noted as a function of dose at 28 days: mean testosterone (\pm SD) was 0.56 (\pm 0.12) and 1.00 (\pm 0.22) in the 3.75 mg group (9 evaluable out of 10 randomised) and 7.5 mg group (4 evaluable out of 5 randomised) respectively.

Assessor's comment:

The accepted mechanism of action of the LHRHa class in prostate cancer is via testosterone suppression or 'medical castration'. The MAH has demonstrated that leuporelin at a dose of 3.75 mg/month or equivalent is associated with testosterone suppression to castrate levels in the majority of patients. The rate and extent of suppression is comparable to goserelin 3.6 mg/month, and to leuporelin 7.5 mg/month. Therefore it is possible to extrapolate data from other LHRH agonists, or from higher doses of leuporelin, to support the proposed neo-adjuvant indication.

Clinical efficacy: prostate volume reduction

An important aim of neo-adjuvant treatment in the radiotherapy setting is to reduce prostate tumour volume and therefore planning volume. This allows the use of increased radiation doses to the tumour, with reduced damage to collateral tissues.

Assessor's comment

It is agreed that a reduction in prostate volume prior to radiotherapy is clinically relevant. The MAH has also submitted studies of neo-adjuvant use prior to radical prostatectomy. This data is relevant when considering prostate volume reduction, since measurements are completed prior to surgery.

The MAH has carried out a literature search to identify studies of leuprorelin in which prostate volume was documented. 13 studies of leuprorelin alone as neo-adjuvant treatment prior to radiotherapy or prostatectomy are submitted. All are single arm open label studies (except one randomised comparison of 3 and 8 months of treatment). A total of 1460 patients were studied. Most studies investigated 3 months of neo-adjuvant treatment (range 1-8 months). Localised and locally advanced prostate cancer patients were included. Endpoints included mean % decrease in prostate volume and proportion of patients with prostate volume reduction. The leuprorelin dose was 3.75 mg/month in 2 studies, 7.5 mg/month in 6 studies and not stated in 5 studies. In the majority of studies, an oral anti-androgen is co-administered. This is standard clinical practice to prevent testosterone flare which may occur at the start of LHRHa treatment.

The MAH has also submitted 6 studies of neo-adjuvant therapy prior to radiotherapy or prostatectomy in which leuprorelin was not the only LHRHa used. Goserelin was the commonest other LHRHa investigated: the overall prostate volume reduction observed in association with leuprorelin or goserelin was 32-35%. In 3 studies, the mean prostate volume reduction in patients taking leuprorelin could be evaluated.

Ten studies of goserelin alone in the neo-adjuvant prostate cancer setting showed prostate volume reductions of 26 – 48%. Duration of treatment was generally 3 months. In the majority of studies a dose of 3.6 mg was used, along with an oral anti-androgen.

Studies of leuprorelin at proposed dose

The most relevant studies for this application are those which investigate a leuprorelin dose of 3.75 mg/monthly or equivalent, in which the effect of leuprorelin can be separated from other LHRH analogues. The 3 studies fitting these criteria are summarised below:

Bourdin et al 1990

In this prospective, single arm study, 40 patients with stages A2 to C prostatic cancer were treated with leuprorelin 3.75 mg/month for 2 months (with flutamide for the first 2 weeks) prior to radiotherapy or radical prostatectomy. The mean age was 71 years. Of 32 evaluable patients, 23 (72%) were classified as 'major responders' on digital rectal examination at 2 months. The prostate volume response was not quantified further. Plasma testosterone levels fell to castration levels (<3 ng/ml) in 39 out of 40 patients after 2 months of leuprorelin treatment.

Assessor's comment:

Stages A2 to C are equivalent to localised and locally advanced prostate cancer.

TAP-144-SR-ENA026 (Prezioso 2004)

In this prospective, open-label, randomised study, 183 patients with stage T1a to T2b prostate cancer, mean age 65 years, were randomised to receive leuprorelin 3.75 mg/month for 3 months (with cyproterone acetate for 3 weeks) or no treatment. After 3 months, all patients underwent radical prostatectomy. 167 patients were evaluated for prostate volume using transrectal echography. Quantitative evaluation was not done. In the leuprorelin arm, 31% of patients demonstrated prostate volume reduction.

Assessor's comment:

This study included only localised prostate cancer.

Kuhn et al 1997

This was a randomised open-label comparative efficacy study of triptorelin and leuprorelin in prostate cancer. 67 patients assessed as unsuitable for surgery, with a mean age of 72 years, were randomly allocated to triptorelin 3.75 mg/month (n=33) or leuprorelin 3.75 mg/month (n=34) for 3 months. transrectal ultrasound (TRUS) to assess prostate volume was carried out at the beginning of the study and at month 3. A reduction in prostate volume was demonstrated in both treatment groups. In the triptorelin group, volume decreased from 40.2 ± 7.7 cm³ (mean \pm SEM) to 19.9 ± 3.5 cm³ for 17 evaluable patients. In the leuprorelin group, volume decreased from 30.9 ± 5.2 cm³ to 26.0 ± 5.2 cm³ in 18 evaluable patients. No statistically significant difference was found between the 2 groups (p = 0.08).

Assessor's comment:

The study enrolled patients with stage B-D disease, which equates to localized and locally advanced disease.

There is a trend towards an increased % reduction in prostate volume for triptorelin compared to leuprorelin (50% vs. 16%). However, only half of the randomised patients were evaluable. In addition, the baseline prostate volume was lower in the leuprorelin arm.

Studies at higher dose than proposed (or dose not stated)

Prostate volume reduction studies at a higher dose of leuprorelin than that approved, or where dose is not stated, are considered supportive. Mean prostate volume reductions of 25-52% were observed. The submitted studies are summarised below:

Solhjem et al 2004

In this observational study, 408 prostate cancer patients undergoing radiotherapy for prostate cancer gave permission for review of their records (out of 427 consecutive patients approached). Mean age was 71.8 years. 122 of the patients received neo-adjuvant hormone treatment, either goserelin or leuprorelin, of which 78 (64%) underwent TRUS before and after neo-adjuvant treatment.

The mean duration of treatment was 4 months (99% received at least 3 months). The mean prostate volume decrease was 31.7%.

Assessor's comment:

Clinical stage was T1c or T2a, equivalent to localised prostate cancer. The dose of leuprorelin is not stated in the study report.

Davis 2013 (post-hoc analyses of Solhjem et al 2005)

This unpublished report provides data from additional patients recruited to the study described above by Solhjem *et al*, and a *post hoc* analysis by LHRH analogue in order to estimate the treatment effect for leuprorelin. Data were reported for a total of 1110 patients with stage T1c/T2a prostate cancer undergoing radiotherapy. 207 received neo-adjuvant treatment of which 189 (91.3%) underwent TRUS prior to treatment and again prior to radiotherapy. Of the 207 patients receiving LHRH agonists, 194 (93.2%) received leuprorelin and 13 (6.8%) received goserelin. The mean treatment duration was 4.9 months: 97.4% received at least 3 months. The mean prostate volume reduction was 36.1%. The mean % volume reduction was 36.5% and 29.8% for the leuprorelin and goserelin groups respectively. Patients treated with goserelin had more advanced disease at baseline.

Assessor's comment:

Not all the 122 patients included in the original report appear to have been included in the updated report since the numbers not undergoing TRUS are inconsistent, and the study commenced one month later.

The dose of leuprorelin is not stated in the study report. However the MAH states that the leuprorelin dose was either 22.5 mg/3 months or 30 mg/4 months. T-stage and Gleason score were inversely correlated with absolute prostate volume reduction.

Andros et al 1993

This prospective single arm study describes the effect of 4 months of neo-adjuvant leuprorelin 7.5 mg monthly (+ anti-androgen) prior to radical prostatectomy in 16 patients, mean age 65 years, with stage C prostate adenocarcinoma. Pre- and post-treatment (prior to surgery) prostate volume was measured by TRUS. The mean reduction was 52% ($p < 0.0001$), from a mean of 60.4 cm³ to a mean of 28.6 cm³.

Macfarlane 1993

In this prospective single arm study, 22 patients with locally advanced prostate cancer (stage B2 to C) received 3 months of leuprorelin 7.5 mg monthly (+ anti-androgen) prior to radical prostatectomy. Prostate volume reduction was assessed by TRUS before the start of androgen deprivation therapy (ADT) and at 12 weeks. The mean prostate volume reduction was 33%.

Zelevsky et al 1994

This prospective single arm study investigated the effect of a 3 month course of leuprorelin (+ anti-androgen) prior to radiotherapy (RT) in 22 patients of median age 71 years and prostate cancer stage T1c – T3. Target volume was measured by computed tomography (CT) CT during treatment planning, before and after neo-adjuvant treatment. The median target volume reduction after neo-adjuvant treatment was 25% (range 3-52%).

Forman et al 1995

In this prospective single arm study, 20 patients with localised prostate cancer (stages T1-2) received 3 months of leuprorelin prior to RT. Prostate volumes pre- and post-hormone treatment were derived from treatment planning CT. The average prostate volume reduction was 37% (range 17 – 57%).

Zelevsky et al 1997

This prospective single arm study investigated the effect of 3 months of neo-adjuvant leuprorelin 7.5 mg monthly (+ anti-androgen) on prostate target volumes assessed by CT, for 45 patients with localised prostate cancer planned for RT. Median age was 69 years. A 27% reduction in target planning volume was observed. Reductions of the volume of rectal wall, bladder wall and bowel exposed to high radiation doses were achieved.

Blasko et al 1997

In this retrospective study, 92 patients with prostate cancer (T1c to T3) received monthly LHRHa (+ anti-androgen) for 3-6 months prior to radiotherapy (RT). Prostate volume pre-and post-treatment were obtained by TRUS. The average prostate volume reduction was 45% (63 cm³ to 34 cm³).

Stock 1998

In this prospective single arm study, 76 patients with prostate cancer (high risk stage T1-T2 disease) received neo-adjuvant leuprorelin (+ anti-androgen) 3 months prior to brachytherapy. Median age was 69 years. In 61 patients, prostate volume was measured by TRUS prior to leuprorelin treatment and prior to radioactive seed implantation. The median volume reduction was 40% (range 6-62%).

Stone et al 1999

This prospective single arm study investigated the effect of 3 months of leuprorelin (+ anti-androgen) prior to brachytherapy in high risk localised prostate cancer (stage 1b-2c). Prostate volume was measured in 106 patients prior to ADT and after 3 months (prior to radioactive seed implant). Mean prostate volume was 50.4 cm³ pre-treatment, and 31.0 cm³ post-treatment, a mean reduction of 35% (range 2 – 62%).

Gleave et al 2001

This prospective open-label parallel randomised controlled trial (RCT) was designed to compare 3 months and 8 months of neo-adjuvant ADT prior to radical prostatectomy in patients with localised prostate cancer. Mean age was 63 years. Treatment was leuprorelin 7.5 mg monthly (+ anti-androgen). 547 patients with stage T1b-T2 were randomised 1:1. Mean prostate volume reduction, assessed by TRUS, was 37% after 3 months (p=0.0001). In the 8 month arm, a further 13% reduction (p=0.03) was observed.

Kucway et al 2002

In this retrospective study, 107 patients with prostate cancer (stage T1b – T3b) received ADT prior to brachytherapy. Median age was 69 years. 101 out of 107 patients received leuprorelin (the majority with an anti-androgen). Prostate volume was assessed with TRUS. Mean prostate volume was reduced by 33% (range 11 – 58%) after a 3.7 month average duration of neo-adjuvant therapy (range 1 – 10 months).

Lorente et al 2003

This was a retrospective study of 200 consecutive localised prostate cancer patients, of which 150 received ADT as leuprorelin (+ anti-androgen) prior to radical prostatectomy. Tumour volume was assessed for surgical specimens. Smaller volume was associated with ADT use, with a significant correlation between treatment

duration and tumour volume. Tumour volume reduction data was unavailable from this study.

Assessor's overall comment on prostate volume reduction studies

Single arm studies are acceptable, since a prostate volume reduction would be unexpected in a placebo arm. The population studies are relevant for the proposed indication. Studies of the proposed dose are considered the most relevant. Three studies fit these criteria, as described above. In *Bourdin et al 1990* and *Prezioso 2004*, prostate volume reduction is observed, but no quantitative estimation is made. In *Kuhn et al 1997*, there is a randomised comparison of leuprorelin and triptorelin. There is a trend towards an increased % reduction in prostate volume for triptorelin compared to leuprorelin (50% vs. 16%). However, only half of the randomised patients were evaluable. In addition, the baseline prostate volume was significantly lower in the leuprorelin arm.

Studies of prostate volume reduction with higher doses of leuprorelin (or dose not stated), and other LHRH analogues can be extrapolated to the proposed dose, given the common mechanism of action via testosterone suppression to castrate levels, and comparable rate and extent of suppression (see *Clinical pharmacology* section). These studies provide more evidence of the likely magnitude of the effect, which is considered clinically relevant.

In conclusion, the submitted studies provide evidence of clinically relevant prostate volume reduction following neo-adjuvant treatment with leuprorelin, and are supportive of efficacy in the proposed indication at the proposed posology.

Clinical efficacy: longer term outcomes

The MAH has submitted published clinical studies of longer term outcomes, including overall survival (OS) following neo-adjuvant LHRH analogue prior to radiotherapy. This includes 4 randomised controlled trials (RCTs) and 6 single arm studies of leuprorelin alone. Four RCTs of leuprorelin and goserelin are also submitted.

Leuprorelin alone

Laverdière et al 1997

The aim of this RCT was to investigate whether ADT (leuprorelin 7.5 mg monthly + flutamide 250 mg TID) as neo-adjuvant treatment prior to RT provided benefit in terms of positive follow-up biopsies and serum prostate specific antigen (PSA) levels at 12 and 24 months post RT. 120 patients with stage T2a – T4 prostate adenocarcinoma were randomised to the following groups:

- Group 1: RT alone
- Group 2: 3 months of neo-adjuvant ADT + RT
- Group 3: 3 months of neo-adjuvant ADT + 6 months of adjuvant ADT + RT.

The patients were stratified according to stage, PSA, and Gleason score.

The results presented were described as an interim analysis. Median age was around 70 years. Baseline characteristics were balanced between treatment groups. 77% and 57% of the randomised patients underwent prostate biopsy and PSA testing at 12 and 24 months post-RT, respectively. The pathology results are summarised in Table 1:

Table 1: Pathological outcomes of biopsy at 12 and 24 months

Biopsy	Group 1		Group 2		Group 3	
	12 months	24 months	12 months	24 months	12 months	24 months
Absence of cancer	10 (29%)	5 (22%)	17 (52%)	18 (72%)	22 (88%)	18 (90%)
Suspicious	2 (9%)	3 (13%)	6 (18%)	0	2 (8%)	1 (5%)
Presence of cancer	21 (62%)	15 (65%)	10 (30%)	7 (28%)	1 (4%)	1 (5%)
Total	33	23	33	25	25	20

p-value at 12 months ($p = 0.00005$). *p*-value at 24 months ($p = 0.00001$).

Table 2: Measurements of median serum PSA levels

Time in months postradiotherapy	Group 1	Group 2	Group 3
12 months	1.56 ng/ml	0.6 ng/ml	0.2 ng/ml
24 months	1.20 ng/ml	0.65 ng/ml	0.5 ng/ml

Assessor's comment:

The study population included localised and locally advanced prostate cancer and is therefore relevant for the proposed neo-adjuvant indication. The dose of leuprorelin was twice that proposed for the new indication.

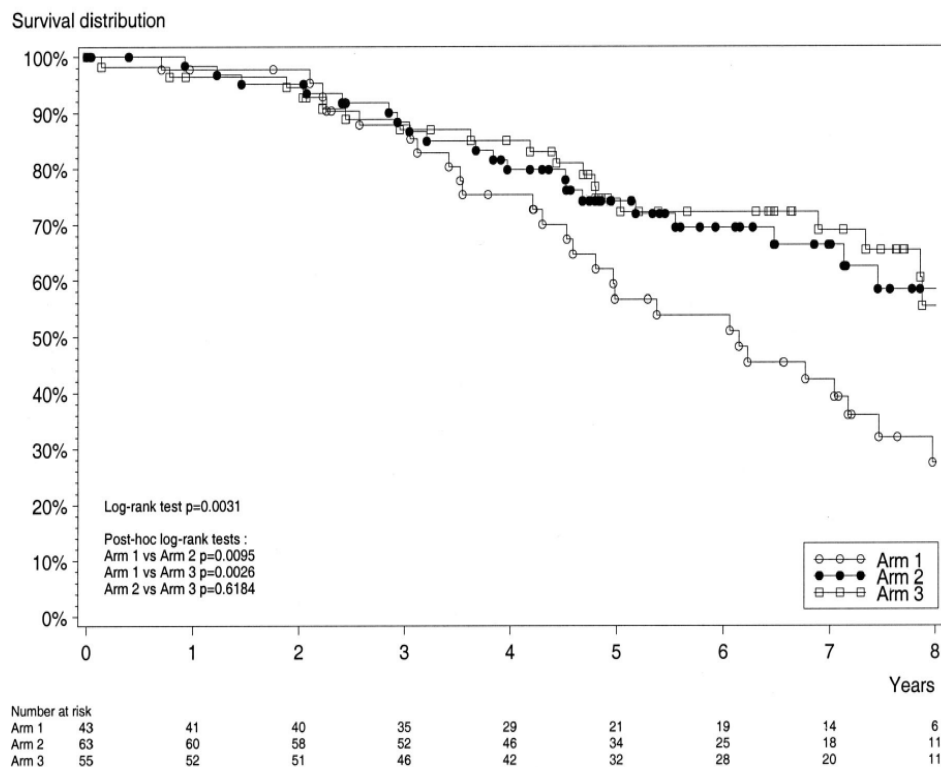
The relevant comparison to support the neo-adjuvant indication is Group 1 versus Group 2. It should be noted that only 77% and 57% of the ITT population respectively were evaluated by biopsy at 12 and 24 months. The authors provide an explanation that some patients refused biopsy and others had not reached the 24 month follow-up visit. Due to the large amount of missing information it is possible that the results shown in Table 1 are biased. If the 'absence of cancer' patients at follow-up biopsy (Table 1) are expressed as a proportion of the ITT population, then a comparison can be made which assumes a worst case scenario *i.e.* those not biopsied had recurrent cancer. In group 1, the proportion of ITT patients without cancer is 24% at 12 months and 12% at 24 months (Statistical Assessor's calculation). The corresponding proportion in group 2 is 40% at 12 months and 42% at 24 months. It is reassuring that this comparison provides some evidence in favour of neo-adjuvant leuprorelin. It is not known whether some patients had dropped out of the study prior to the 12 and 24 months follow-up, and if so whether dropouts were related to treatment allocation. The PSA outcomes (Table 2) provide some supportive evidence of benefit for neo-adjuvant leuprorelin (Group 2 versus Group 1). However, the numbers evaluated are not known.

Laverdière et al 2004

This paper presents data from 161 patients enrolled and randomised into study 1 (presented above as an interim analysis of 120 patients), and 325 patients enrolled and randomised into study 2. Eligible patients had stage T2-T3 prostate cancer. Study 2 compared neo-adjuvant and neo-adjuvant + adjuvant ADT. Endpoints included 'no biochemical evidence of disease'.

In study 1, at a median follow-up of 5 years, 7-year biochemical-free survival rates were 42%, 66% and 69% in groups 1 to 3 respectively ($p=0.009$ for the comparison of groups 1 and 2). Multivariate analysis showed a hazard ratio of 0.5 for group 1 vs. group 2 ($p=0.01$).

Figure 3: overall PSA progression-free survival of 161 randomised patients in study 1



Overall PSA progression-free survival of 161 randomized patients in study 1. Arm 1 received EBRT alone, arm 2 received neoadjuvant AS with EBRT and arm 3 received neoadjuvant and adjuvant AS with EBRT. Significance difference was found between arms 1 and 2, and 1 and 3. No statistical difference was observed between arms 2 and 3.

Assessor's comment:

Laverdière et al 2004 provides additional data from the study described by *Laverdière et al 1997* additional patients are included, and PSA progression-free survival is presented. It is not known how well this endpoint correlates with OS, or quality of life.

The other 3 RCTs of leuprorelin alone are not designed to demonstrate the efficacy of leuprorelin as neo-adjuvant treatment prior to RT:

- *TROG 04.04 RADAR trial (Denham 2012)* is a comparison of neo-adjuvant leuprorelin vs. neo-adjuvant + adjuvant leuprorelin.
- *TAP/III/98/032 (Mottet 2012)* is a comparison of leuprorelin alone vs. leuprorelin + RT
- *SPCG-7/SFUO3 (Widmark 2009; Fransson 2009)* is a comparison of leuprorelin alone vs. leuprorelin + RT

The 6 single arm studies of leuprorelin alone, as neo-adjuvant treatment prior to radiotherapy or prostatectomy demonstrate favourable activity for surrogate endpoints such as PSA and testosterone levels. Disease free survival and overall survival data are

also provided, but the added benefit of neo-adjuvant leuprorelin, over RT alone, cannot be estimated.

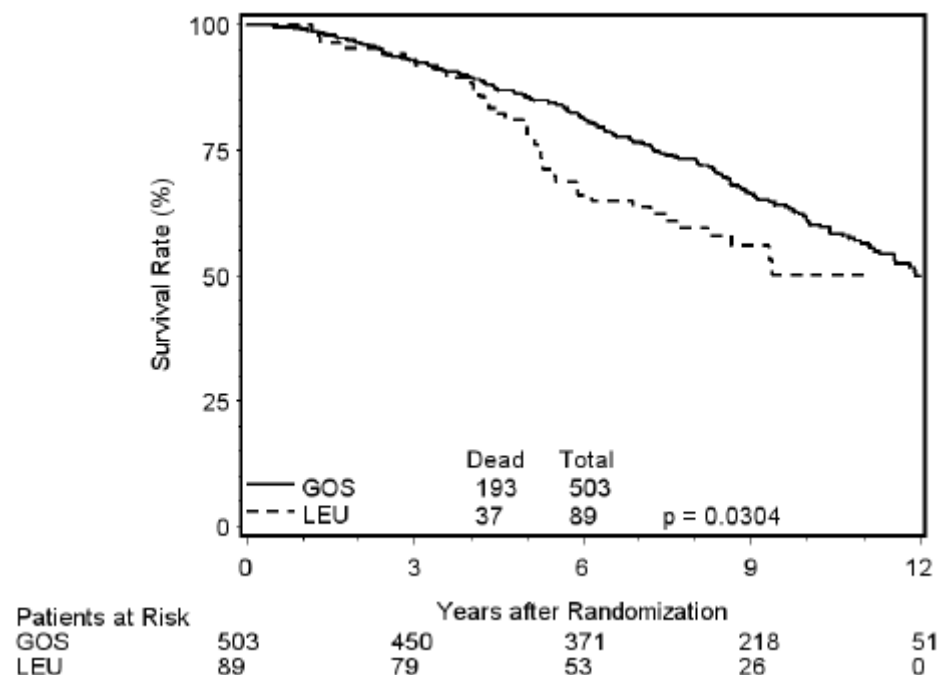
Leuprorelin and goserelin

The 4 RCTs of goserelin and leuprorelin provide some relevant data for the leuprorelin neo-adjuvant indication, and are summarised below:

RTOG 94-08 (Jones et al 2011)

This was a RCT designed to investigate the effect of ADT on cancer control and OS when used before and during RT. Between 1994 and 2001, 2028 patients with stages T1b – T2b (PSA \leq 20ng/ml) were randomised 1:1 to RT alone, or RT + 4 months of ADT (starting 2 months prior to RT). ADT was goserelin 3.6 mg monthly or leuprorelin 7.5 mg monthly. All ADT patients received flutamide. The primary endpoint was OS. The treatment groups were balanced, with a median age of around 70 years. Median follow-up was 9.1 years. The 10 year OS was 62% for those receiving ADT+RT compared to 57% for those receiving RT alone (HR 1.17; 95% CI 1.01-1.35; $p = 0.03$). The ADT+RT arm was also favoured for all secondary endpoint (disease-specific mortality, biochemical failure, distant metastases, and rate of positive findings on prostate biopsy at 2 years). Disease specific mortality was 8% in the radiotherapy-alone group and 4% in the combined-therapy group (hazard ratio = 1.87; 95% CI, 1.27 to 2.74; $P = 0.001$).

A post hoc analysis of the dataset used for the *Jones et al 2011* publication was carried out by *Dignam 2013* in order to compare efficacy and safety for the subgroups receiving leuprorelin versus goserelin in the ADT+RT arm. The MAH states that the data analyses required were agreed before the analyses commenced. Analysis of disease outcomes were carried out among patients identified as intermediate and high risk in the original study (there was no significant benefit from ADT in low risk patients in RTOG 94-08). Of patients at intermediate and high risk, 503 received goserelin only, and 89 received leuprorelin only. The 10 year OS estimates were 60.9% and 50.2% for goserelin and leuprorelin respectively. The hazard ratio for overall survival favoured goserelin (HR = 1.48; 95% CI 1.04-2.11; $p = 0.03$). Adjusting for potential confounders of performance score, age, initial PSA, grade and nodal status did not have a significant effect. There was an increased rate of secondary cancers in the leuprorelin group (15.8% vs. 7.7%), but no difference between groups for prostate cancer-specific mortality or deaths from non-cancer or unknown causes. The hazard ratio for biochemical failure was in favour of leuprorelin (HR = 0.53; 95% CI 0.30 – 0.91; $p = 0.02$). The rates of distant metastases were similar between groups.

Figure 4: Kaplan-Meier OS curves for goserelin and leuprorelin groups (intermediate and high risk patients)**Assessor's comment:**

Only patients with localised prostate cancer were investigated. The dose of leuprorelin was twice that proposed for the new neo-adjuvant indication. RTOG 94-08 demonstrated a statistically and clinically significant benefit in terms of overall survival, for the use of neo-adjuvant ADT prior to radiotherapy. However, it is not possible to determine the relative contribution of leuprorelin to this benefit, based on the published data. The *post hoc* analysis of *Dignam 2013* compared the outcomes between patients receiving leuprorelin vs goserelin, in the ADT+RT arm. The OS analysis favoured goserelin, but this may have been due to an increased rate of deaths from second primary cancers in the leuprorelin group, which is likely to be a chance finding rather than a drug-related toxicity. This is supported by the K-M curves (fig 4) which show separation after around 4 years. Secondary outcomes including biochemical failure rate were less supportive of superiority of goserelin. The 10 year survival rates for the intermediate and high groups were 54% and 51% in the RT alone arm. It should be noted that the allocation to goserelin or leuprorelin was not randomised, and the factors influencing choice of ADT are unknown.

D'Amico et al (2004, 2008)

The objective of this open-label RCT was to assess the survival benefit of RT alone or in combination with 6 months of ADT in patients with high risk localised prostate cancer. The main outcome measure was time to all-cause mortality. 206 patients with stage T1b to T2b disease (PSA \geq 10 ng/ml or gleason \geq 7) were randomised 1:1, stratified according to PSA, Gleason score or MRI evidence of extra-capsular extension. Median age was 72.5 years. ADT was given for 2 months prior to RT, and was a combination of LHRH analogue (leuprorelin 7.5 mg/month or goserelin 3.6 mg/month) and an anti-androgen (flutamide). ADT was recommended on development of PSA failure (PSA \geq 10ng/ml). 88 patients received leuprorelin and 10

patients received goserelin (3 withdrew consent and 1 had T2c disease). The median follow-up was 7.6 years. A significant increase in the risk of all-cause mortality (44 vs 30 deaths; HR = 1.8; 95% CI 1.1-2.9; P=0.01) was observed in men randomized to RT compared with RT and ADT. Of the 18 deaths attributable to prostate cancer, 14 and 4 occurred in men randomised to RT and RT+ADT respectively. The 8 year overall survival estimates were 74% and 61% respectively (p = 0.01). There appeared to be greater benefit in patients with no or minimal comorbidity, based on sub-group analyses.

Assessor's comment:

Only patients with localised prostate cancer were investigated. The dose of leuprorelin was twice that proposed for the new neo-adjuvant indication. This study demonstrated a statistically and clinically significant benefit in terms of overall survival, for the use of neo-adjuvant ADT prior to radiotherapy. It is not possible to determine the relative contribution of leuprorelin to this benefit, based on the published data. However, given that only 10 out of the 98 patients treated with ADT received goserelin, it is unlikely that the treatment effect was driven by goserelin. Therefore this study provides evidence of efficacy of leuprorelin in the neo-adjuvant indication, in terms of OS, although at a higher dose than that proposed in this application.

Medical Research Council (MRC) RT01 (Dearnaley et al 2007,2011; Sydes 2004; Stephens et al 2006; Syndikus et al 2010)

This trial was designed to compare conformal radiotherapy with conventional radiotherapy. All patients received neo-adjuvant ADT, either leuprorelin 3.75 mg monthly or goserelin 3.6 mg monthly. Patients with T2-T4 (N0, NX or M0) disease. T2 patients had PSA \geq 40 mg/ml or \geq 20 ng/ml with Gleason score $>$ 8.

Assessor's comment:

The relative numbers receiving leuprorelin or goserelin are not reported. It is not possible to compare outcomes for patients who took neo-adjuvant leuprorelin relative to goserelin. However this MRC study provides evidence of established clinical use.

NCIC CTG PR.3/MRC UK PR07 (Warde et al 2011)

This RCT was designed to investigate the additional benefit of RT over and above long-term ADT in high risk localised or locally advanced prostate cancer (T2 – T4), and does not therefore provide evidence of the benefit of neo-adjuvant ADT. Median age was around 70 years. All patients were started on lifelong ADT before randomisation, either bilateral orchidectomy or LHRH analogue according to preference. 1205 patients were randomised 1:1 to ADT+TR or ADT alone. The RT arm received RT within 8 weeks of randomisation. The primary outcome measure was overall survival. LHRH agonists were used as ADT in 92% of patients. The addition of RT to ADT resulted in significantly improved overall survival (HR 0.77; 95% CI 0.61-0.98; p=0.03).

Paruleker 2013 has conducted a *post hoc* analysis of the above study, in order to compare the relative treatment effects of leuprorelin and goserelin in the RT+ADT arm. The MAH states that the data analyses required were agreed before the analyses commenced. Of the 603 allocated to RT+ADT, 86 received leuprorelin (the majority 3.75 mg/month) and 402 received goserelin (the majority 3.6 mg/month) prior to RT.

The ECOG scores at baseline differed between the leuprorelin and goserelin sub-groups, in favour of goserelin:

Table 3: ECOG performance at baseline

ECOG Performance	Goserelin (n,%)	Leuprorelin (n,%)
0	328 (81.6%)	59 (68.6%)
1	68 (16.9%)	25 (29.1%)
2	6 (1.5%)	2 (2.3%)

The median duration of LHRH agonist treatment prior to RT was 48 days. Median OS was estimated at 10.99 years (95% CI 9.78 – 13.3) and 9.95 years (95% CI 8.78 - ∞) for goserelin and leuprorelin respectively. The hazard ratio was 1.182 in favour of goserelin (95% CI 0.80 – 1.75).

Assessor's comment:

It should be noted that the allocation to goserelin or leuprorelin was not randomised, and the factors influencing choice of ADT are unknown. Although the RT arm patients received ADT prior to randomisation, the period of neo-adjuvant treatment was not standardised. The dose of leuprorelin was generally 3.75 mg/month, in line with the proposed posology for the neo-adjuvant indication. In the post-hoc analysis population, the median duration of treatment was around 7 years. Therefore, any efficacy comparison of leuprorelin vs. goserelin relates to adjuvant, as well as the neo-adjuvant, treatment. There appears to be an OS trend in favour of goserelin. However the numbers receiving leuprorelin are relatively small and the data are immature, as shown by the confidence interval around the OS estimate for leuprorelin. It should also be noted that the ECOG performance at baseline favoured goserelin.

Goserelin alone

The MAH has also submitted RCTs which investigate goserelin as neo-adjuvant treatment prior to radiotherapy:

- *RTOG 86-10 (Pilepich 2001, Roach 2003)*: in patients with locally advanced prostate cancer, 4 months of neo-adjuvant goserelin prior to RT was compared to RT alone. Long-term endpoints favoured neo-adjuvant ADT, although overall survival differences were not statistically significant.
- *TROG 96-01 (Denham 2005, 2011)*: this study compared 3 or 6 months of goserelin prior to RT with RT alone, in patients with high risk localised and locally advanced prostate cancer. All-cause mortality was statistically significantly improved in patients in the 6 month arm compared to RT alone, whereas only a trend was evident in the 3 month arm.
- *Crook 2004*: this study compared the effects of 3 month and 8 months of neo-adjuvant goserelin prior to RT. Treatment failure rates were similar between groups.

Assessor's comment:

The MAH has submitted published clinical studies of longer term outcomes, including OS, following neo-adjuvant LHRHa prior to radiotherapy. An RCT of leuprorelin

alone (Laverdière et al 1997,2004) was conducted at twice the proposed dose in patients with localised and locally advanced prostate cancer. This study provides evidence of benefit for outcomes including positive re-biopsy and PSA progression-free survival, but not OS or quality of life. Single arm studies of leuprorelin alone provide some evidence of benefit in terms of PSA and testosterone levels.

Randomised controlled trials of leuprorelin or goserelin investigate the effect of neo-adjuvant treatment prior to RT on overall survival. In one study (RTOG 94-08) which used leuprorelin at twice the proposed dose in localised prostate cancer, an OS advantage for neo-adjuvant LHRHa was demonstrated. In a post-hoc analysis by LHRHa, the hazard ratio for OS favoured goserelin whereas the hazard ratio for biochemical failure was in favour of leuprorelin. It seems likely that the increased incidence of secondary cancers in the leuprorelin arm occurred by chance, and explains the OS difference. In another RCT of neo-adjuvant leuprorelin or goserelin in which almost 90% of patients with localised prostate cancer received leuprorelin (D'Amico et al 2004, 2008), at twice the proposed dose, use of neo-adjuvant LHRHa prior to RT was associated with increased overall survival. The MAH has also submitted RCTs of goserelin alone as neo-adjuvant therapy prior to RT, in high risk localised and locally advanced prostate cancer which provide evidence of efficacy of LHRHa with regards to long term clinical endpoints including OS.

Much of the longer term data comes from studies of leuprorelin at a higher dose than that proposed, or goserelin. However it is acceptable to extrapolate data from studies investigating higher doses of leuprorelin, or other LHRH analogues, in view of the common mechanism of action via testosterone suppression to castrate levels, and comparable rate and extent of suppression. Overall, the longer term data, which includes overall survival, are supportive of efficacy in the proposed indication at the proposed posology.

Guidelines

The MAH refers to 4 treatment guidelines in support of a neo-adjuvant indication:

NICE 2008 – Prostate cancer: diagnosis and treatment

In this guideline, the management of high-risk localised prostate cancer (i.e. Gleason score ≥ 8 , or PSA > 20) is considered under the heading of locally advanced disease. The guideline recommends neo-adjuvant and concurrent LHRHa therapy for 3 to 6 months in men receiving radical radiotherapy for locally advanced prostate cancer. The evidence comes from a systematic review by *Kumar et al 2006*. No recommendation is made to use any particular LHRHa.

European Association of Urology (EAU) Guidelines on Prostate Cancer . Part 1: Screening, Diagnosis and Treatment of Clinically Localised Disease

In high risk localised prostate cancer, short-term ADT before and during radiotherapy results in increased OS. In patients with T2c-T3N0-x (Gleason score 6), short-term ADT before and during RT may favourably influence OS.

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Neo-adjuvant LHRHa therapy for 3-6 months is recommended for men receiving radical radiotherapy for high-risk disease. No recommendation is made to use any particular LHRHa.

MDT Guidance for Managing Prostate Cancer 2013 (British Uro-oncology Group, British Association of Urological Surgeons: Section of Oncology)

Neo-adjuvant hormone therapy reduces prostate volume by 30-40%. This can reduce the size of the treatment field and as a result the level of toxicity experienced. Neo-adjuvant ADT prior to RT is a treatment option for high risk localised and locally advanced disease.

Safety aspects

Safety data for leuprorelin as neo-adjuvant treatment prior to radiotherapy or radical prostatectomy are available from 5 studies of prostate volume in which a total of 958 patients were exposed. Safety data are also available from 7 longer term studies in 2608 patients exposed to leuprorelin in the neo-adjuvant to RT setting. A further 221 patients were exposed to leuprorelin, as identified in post-hoc analyses of 2 studies of leuprorelin and goserelin. Data for goserelin in the neo-adjuvant to RT setting from RTOG 86-10 are also available for comparison. The duration of treatment was 3 months in the majority of studies (range 2 to 9 months). In the majority of studies, treatment was continued during RT. Doses were 3.75 mg monthly, 7.5 mg monthly, 11.25 mg 3-monthly, 22.5 mg 3-monthly or 30 mg 4-monthly.

Prostate volume reduction studies

In studies of leuprorelin prior to radiotherapy or radical prostatectomy, reported adverse events included hot flushes, impotence, erectile dysfunction, increased perspiration, asthenia, rash, nausea, urinary leakage and thrombosis. No grade 3/4 events were observed following RT. Similar adverse events were reported in studies of goserelin and triptorelin in the same treatment setting.

Longer term clinical studies of neo-adjuvant leuprorelin prior to RT

Study TAP/III/98/032 compared the combination of leuprorelin 11.25 mg 3 monthly + RT to leuprorelin alone in 264 patients with locally advanced prostate cancer. 131 patients received leuprorelin alone, of which 67.2% reported vascular disorder (primarily hot flushes), 18.3% reproductive system and breast disorders, and 11.5% reported renal and urinary toxicities. Treatment related SAEs were reported for 3 patients: arthritis, syncope and thrombophlebitis. In a similar study evaluating RT in addition to ADT (Widmark 2009), 875 patients received leuprorelin alone for 3 months. At 4 years, 12% reported urinary problems, 7% bowel symptoms and 72% erectile dysfunction. SAEs were reported in 11 patients. It should be noted that patients were continued on anti-androgen therapy until progression, and treated with leuprorelin once PSA progression had occurred.

Assessor's comment:

In the majority of studies, it is not possible to attribute adverse events to neo-adjuvant treatment alone. Many events are likely to result from RT, adjuvant hormonal treatment, treatments after progression, or the disease itself.

Longer term clinical studies of neo-adjuvant leuprorelin or goserelin prior to RT

In the RTOG 94-08 randomised controlled study comparing radiotherapy plus short-term ADT to radiotherapy alone, locally advanced prostate cancer patients received leuprorelin or goserelin for androgen suppression for 2 months prior to and 2 months during radiotherapy (Jones 2011). In the group receiving ADT, 29% reported hepatic toxic effects, of which 20% were grade 1. Grade 3 or higher gastrointestinal toxicity was reported by 1%, and genitourinary toxicity by 2%. Late hepatic, gastrointestinal and genitourinary toxicity was reported by 6%, 3% and 8% respectively. During the 8 weeks of ADT prior to RT, 55% reported hot flushes, 3% rash, 16% hepatic toxicity, 16% decreased haemoglobin, and 4% elevated white cell count. 1% reported late grade 1 cardiac toxicity within 2 years. In the post-hoc analysis of RTOG 94-08 (Dignam 2013), safety data was compared for the 135 patients treated with leuprorelin and the 769 patients treated with goserelin. Prior to RT, both ADT groups reported hot flushes, gastrointestinal effects, hepatic toxicity, reduced haemoglobin and rash, with similar incidences:

Table 4: Toxic effects attributed to hormone therapy (prior to RT)

	Goserelin (n=769)	Leuprorelin (n=135)
GI	351 (45.6%)	65 (48.1%)
Hot Flashes	440 (57.2%)	75 (55.6%)
Rash	20 (2.6%)	2 (1.5%)
Hepatic Toxicity	121 (15.7%)	26 (19.3%)
Elevated WBC	36 (4.7%)	0 (0.0%)
Decreased HGB	128 (16.6%)	20 (14.8%)
Cardiac toxicity within two years after protocol treatment (present, not graded)	23 (3.0%)	3 (2.2%)

Assessor's comment:

In RTOG 94-08, patients assigned to ADT also received flutamide, which is associated with hepatotoxicity.

The RCT reported by D'Amico (2004, 2008) compared RT+ADT with RT alone, in 206 patients with high risk localised prostate cancer. 88 out of 98 patients received goserelin. ADT was administered for 6 months, of which 2 months was neo-adjuvant. For men potent at baseline, 34% reported impotence in the ADT+RT group, compared to 31% in the RT alone group; grade 3 impotence was reported in 27% and 20% respectively. Gynaecomastia (grade 1-2) was reported by 18% and 3% respectively. Other toxicities were reported with similar frequencies in both ADT+RT and RT alone groups, except for rectal bleeding which was reduced in the ADT+RT group.

In the MRC RT01 trial, 2 doses of RT were compared. All patients received neo-adjuvant therapy with leuprorelin or goserelin for 3-6 months prior to and during RT. After the start of neo-adjuvant ADT, but prior to RT, there was an increase in erectile dysfunction; bladder and bowel function were largely unchanged compared to baseline. Quality of life was evaluated for 321 patients during the neo-adjuvant treatment period: a detrimental effect on sexual functioning, but not urinary function was observed.

Assessor's comment:

The safety profile of leuprorelin is well-established, for long-term use in the currently approved indications. The MAH has submitted safety data from the literature to support the proposed neo-adjuvant indication. The submitted data covers the high-risk localised and locally advanced prostate cancer populations. The studies doses are equivalent to 3.75 mg per month or greater, and are therefore relevant. The exposures are adequate for the neo-adjuvant indication.

The types of adverse effects observed with short-term use of leuprorelin prior to RT are expected in view of the known pharmacology of LHRHa: hot flushes, erectile dysfunction, gastrointestinal effects and gynaecomastia. From the available data, the safety profile in the neo-adjuvant indication is comparable to goserelin.

Evaluation

The accepted mechanism of action of the LHRHa class in prostate cancer is via testosterone suppression or 'medical castration'. The MAH has demonstrated that leuprorelin at a dose of 3.75 mg/month or equivalent is associated with testosterone suppression to castrate levels in the majority of patients. The rate and extent of suppression is comparable to goserelin 3.6 mg/month, and to leuprorelin 7.5 mg/month. Therefore it is possible to extrapolate data from other LHRH agonists or from higher doses of leuprorelin, to support the proposed neo-adjuvant indication.

An important aim of neo-adjuvant treatment in the radiotherapy setting is to reduce prostate tumour volume and therefore planning volume. This allows the use of increased radiation doses to the tumour, with reduced damage to collateral tissues. Studies of prostate volume reduction at the proposed dose of 3.75 mg/month provide mainly qualitative evidence of prostate volume reduction. However it is acceptable to extrapolate data from studies investigating higher doses of leuprorelin, or other LHRH analogues, in view of the common mechanism of action via testosterone suppression to castrate levels, and comparable rate and extent of suppression. These studies provide more evidence of the likely magnitude of the effect, which is considered clinically relevant. It is concluded that the submitted studies provide evidence of clinically relevant prostate volume reduction following neo-adjuvant treatment with leuprorelin, and are supportive of efficacy in the proposed indication at the proposed posology.

The MAH has submitted published clinical studies of longer term outcomes, including OS, following neo-adjuvant LHRHa prior to radiotherapy. An RCT of leuprorelin alone (Laverdière et al 1997, 2004) was conducted at twice the proposed dose in patients with localised and locally advanced prostate cancer. This study provides evidence of benefit for outcomes including positive re-biopsy and PSA progression-free survival, but not OS or quality of life. Single arm studies of leuprorelin alone provide some evidence of benefit in terms of PSA and testosterone levels.

Randomised controlled trials of leuprorelin or goserelin investigate the effect of neo-adjuvant treatment prior to RT on overall survival. In one study (RTOG 94-08) which used leuprorelin at twice the proposed dose in localised prostate cancer, an OS advantage for neo-adjuvant LHRHa was demonstrated. In a post-hoc analysis by

hormone treatment, the hazard ratio for OS favoured goserelin whereas the hazard ratio for biochemical failure was in favour of leuprorelin. It seems likely that the increased incidence of secondary cancers in the leuprorelin arm occurred by chance, and explains the OS difference. In another RCT of neo-adjuvant leuprorelin or goserelin in which almost 90% of patients with localised prostate cancer received leuprorelin (D'Amico et al 2004, 2008), at twice the proposed dose, use of neo-adjuvant LHRHa prior to RT was associated with increased overall survival. The MAH has also submitted RCTs of goserelin alone as neo-adjuvant therapy prior to RT, in high risk localised and locally advanced prostate cancer which provide evidence of efficacy of LHRHa with regards to long term clinical endpoints including OS.

Much of the longer term data comes from studies of leuprorelin at a higher dose than that proposed, or goserelin. However it is acceptable to extrapolate data from studies investigating higher doses of leuprorelin, or other LHRH analogues, in view of the common mechanism of action via testosterone suppression to castrate levels, and comparable rate and extent of suppression. Overall, the longer term data, which includes overall survival, are supportive of efficacy in the proposed indication at the proposed posology.

The safety profile of leuprorelin is well-established, for long-term use in the currently approved indications. The MAH has submitted safety data from the literature to support the proposed neo-adjuvant indication. The submitted data covers the high-risk localised and locally advanced prostate cancer populations. The studied doses are equivalent to 3.75 mg per month or greater, and are therefore relevant. The exposures are adequate for the neo-adjuvant indication. The types of adverse effects observed with short-term use of leuprorelin prior to RT are expected in view of the known pharmacology of LHRHa: hot flushes, erectile dysfunction, gastrointestinal effects and gynaecomastia. Longer term toxicities observed in the submitted studies cannot be attributed specifically to neo-adjuvant use alone; many events are likely to result from RT, adjuvant hormonal treatment, treatments after progression, or the disease itself. From the available data, the safety profile in the neo-adjuvant indication is comparable to goserelin.

Conclusion on proposed variations to Sections 4.1 and 5.1 of the SmPC

The bibliographic evidence submitted is adequate to support the proposed new indication as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer. The accepted mechanism of action of the LHRHa class in prostate cancer is via testosterone suppression or 'medical castration'. Therefore it is possible to extrapolate data from other LHRH agonists, or from higher doses of leuprorelin. The safety of leuprorelin in the proposed indication is expected to be similar to or better than the established profile, since the population is not new and use is relatively short-term. The benefits of neo-adjuvant treatment prior to radiotherapy, in terms of prostate volume reduction, an increase in PSA progression free survival and overall survival are expected to outweigh the risks.

Overall Conclusion

The outstanding issues have been addressed by the Applicant. The updated product information is acceptable. The variation is therefore approvable.

Decision - Grant

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated

Following approval of the variation on 24th May 2014 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

ANNEX 2

Our Reference:	PL 16189/0012-0025
Product:	PROSTAP® SR DCS 3.75 mg Powder and Solvent for Prolonged-release Suspension for Injection in Pre-filled Syringe
Marketing Authorisation Holder:	Takeda UK Limited
Active Ingredient(s):	Leuprorelin acetate
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	N/A

Reason:

To update section 4.2 (posology and administration) of the SmPC to reflect the recent developments in the treatment of castrate-resistant prostate cancer (CRPC) and current medical practice with consequential update to section 5.1 (pharmacodynamics) of the SmPC concerning results obtained in recent clinical trials of new therapies added to GnRH analogue treatment in patients with metastatic CRPC. As a consequence, the Health Professional Leaflet has been updated.

Supporting Evidence

The MAH has submitted a clinical overview with references, to support the proposed changes. The overview is signed by a medically qualified expert.

Section 4.2

The proposed additional text is as follows:

In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer. Reference should be made to relevant guidelines.

The amendment to Section 4.2 is intended to reflect recent developments in the treatment of castrate resistant prostate cancer (CRPC) and current medical practice in accordance with relevant clinical treatment guidelines. In addition the SmPC Guideline (2009) states that information on the duration of use can be included if relevant.

Section 5.1

The proposed additional text is as follows:

In patients with metastatic castration resistant prostate cancer, clinical studies have shown benefit from the addition of agents such as the androgen axis inhibitors abiraterone acetate and enzalutamide, the taxanes docetaxel and cabazitaxel, the

immunotherapeutic agent sipuleucel-T and the radiopharmaceutical Ra-223 to GnRH agonists such as leuprorelin.

The amendment is proposed as a corollary of the amendment to Section 4.2, and concerns the results of recent clinical trials of new therapies added to GnRH analogue treatment in CRPC.

Evidence

Treatment guidelines recommend that non-orchidectomised CRPC patients should remain on GnRH analogues regardless of additional therapies. For example, the NICE guideline 'Prostate Cancer; diagnosis and treatment' (2014) states 'Even when the disease becomes hormone relapsed the androgen receptor on the cancer cells can remain active and LHRHa therapy is usually continued.'

The MAH also presents literature data referred to by guidelines recommending continuation. Androgen stimulation in CRPC is associated with a worse outcome (Manni et al 1988). In a retrospective analysis, continued medical or surgical androgen suppression in CRPC was associated with improved survival outcomes (Taylor et al 1993).

In the pivotal clinical trials of agents approved in metastatic CRPC (abiraterone, enzalutamide, cabazitaxel, docetaxel, sipuleucel-T and radium-223), all non-orchidectomised patients were maintained on androgen deprivation therapy (ADT). In addition, the SmPCs of abiraterone and enzalutamide recommend that medical castration with an LHRH analogue should be continued during treatment in non-orchidectomised patients.

Evaluation

Section 4.2

The SmPC Guideline (2009), makes the following recommendation for Section 4.2, of relevance for this variation application:

Where appropriate, a reference to official recommendations should be made.

Where appropriate, the following points should be addressed:

[.....]

- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation

[.....]

It is agreed that advice to continue GnRH analogue treatment in CRPC patients is in line with current treatment guidelines. It is also agreed that the inclusion of such advice is in line with the SmPC Guideline, and might be useful to prescribers. Furthermore, identical wording is included in the SmPCs of triptorelin products.

Section 5.1

The SmPC guideline (2009) states 'It is not in the remit of the SmPC to give general advice on the treatment of particular medical conditions.' The proposed wording is considered general advice.

In addition, the following guidance is provided regarding the inclusion of information relating to clinical efficacy and safety in Section 5.1:

‘It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication.’

The proposed additional wording is not considered appropriate for inclusion in Section 5.1, since the data referred to was not generated during the pivotal trials supporting the indication in metastatic prostate cancer. In addition, the data does not provide additional evidence of the efficacy of GnRH analogues in CRPC since GnRH analogues were used in all patients.

Conclusion

The proposed variation to Section 4.2 is acceptable.

The proposed variation to Section 5.1 is not in line with the SmPC (2009) guideline. No additional wording in section 5.1 is required to support the variation to section 4.2. The applicant has agreed not to include additional wording in section 5.1 as part of this variation. Therefore only section 4.2 will be varied. The proposed additional wording is acceptable.

Decision - Approved on 12 June 2015.