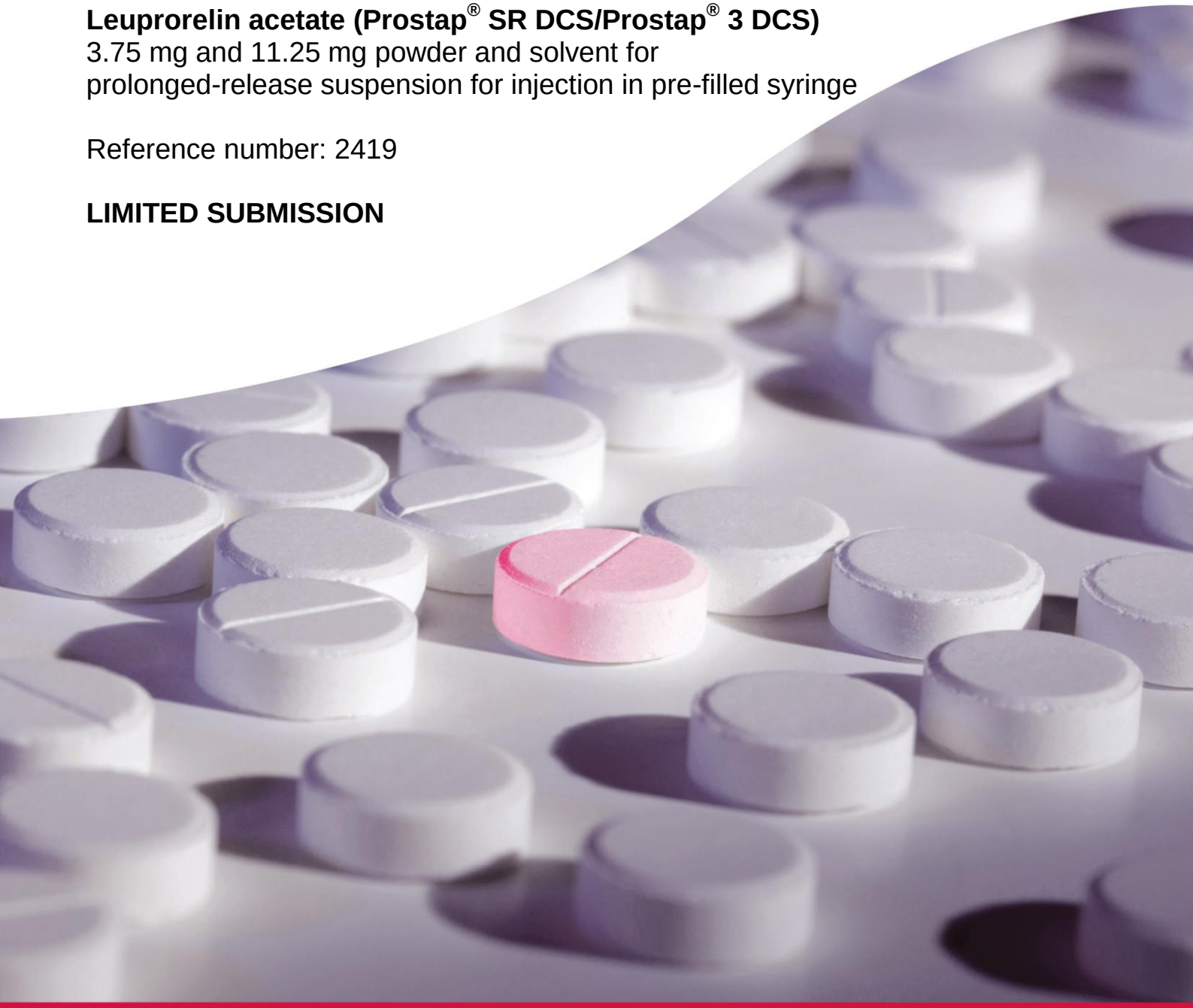
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS)
3.75 mg and 11.25 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

Reference number: 2419

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) 3.75 mg and 11.25 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe. Reference number: 2419. October 2014.

AWMSG Secretariat Assessment Report
Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) 3.75 mg and 11.25 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

This assessment report is based on evidence from a limited submission by Takeda UK Ltd on 24 June 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) as neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer[2,3].
Dosing	The usual recommended dose of leuprorelin acetate (Prostap® SR DCS) is 3.75 mg presented as a one month depot injection and administered as a single subcutaneous or intramuscular injection every month. The usual recommended dose of leuprorelin acetate (Prostap® 3 DCS) is 11.25 mg presented as a three month depot injection and administered as a single subcutaneous injection at intervals of three months. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2,3].
Marketing authorisation date	24 May 2014[2,3] (licensed for the original indication on 28 April 2011[4–6]).
Comparators	The comparator included in the company submission was goserelin (Zoladex®).
Limited submission details	Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company identified a number of publications where both leuprorelin acetate and the comparator, goserelin, had been used in the neoadjuvant setting within the same clinical trial. The company approached the authors of the identified publications to establish if they were willing to participate in a post hoc analysis to provide comparative data between leuprorelin acetate and goserelin in this setting. Three authors agreed to participate and these publications were therefore included in the post hoc analysis[1].

2.1 Post hoc analysis of published studies

2.1.1 Post hoc analysis of Solhjem et al (2004)

An unpublished post hoc analysis[7] was performed to estimate the treatment effect for leuprorelin acetate versus goserelin[4,6]. In the post hoc analysis, 207 patients received neoadjuvant treatment; 194 (93.2%) received leuprorelin acetate and 13 (6.8%)

received goserelin[1,4,6,7]. The mean treatment duration was 4.9 months[4,6,7]. The mean percent reduction in prostate volume was 36.5% and 29.8% for the leuprorelin acetate and goserelin groups, respectively. There was no statistically significant difference between the mean of both groups (p = 0.18)[1].

2.1.2 Post hoc analysis of Warde et al (2011)

A post hoc analysis[8] was carried out to compare the relative treatment effects of leuprorelin acetate and goserelin in the combined treatment arm (androgen deprivation therapy [ADT] plus radiotherapy)[4,6]. Of the patients (n = 603) allocated to receive ADT plus radiotherapy, 86 patients received leuprorelin acetate and 402 patients received goserelin prior to radiotherapy. The primary endpoint was overall survival (OS). The median OS was estimated at 10.99 years (95% confidence interval [CI]: 9.78 to 13.3) and 9.95 years (95% CI: 8.78 to infinity) for goserelin and leuprorelin acetate, respectively[1,4,6,8]. The company reported that the post hoc analysis did not demonstrate any outcome differences between those patients receiving leuprorelin acetate or goserelin in the combined treatment arm[1].

2.1.3 Post hoc analysis of Jones et al (2011)

The post hoc analysis[9] compared men receiving either leuprorelin acetate or goserelin in the combined treatment arm that were considered to be either intermediate- or high-risk. 503 patients received goserelin and 89 patients received leuprorelin acetate. The 10-year OS rates were in favour of goserelin (60.9% versus 50.2%; hazard ratio [HR]: 1.48; 95% CI: 1.04 to 2.11; p = 0.0304)[1,4,6,9]. The lower 10-year OS observed in the leuprorelin acetate group was thought to be due to the increased rate of secondary cancers in the leuprorelin acetate group; these were not considered to be related to prostate cancer or leuprorelin acetate[1,4,6]. Clinical outcome data in the post hoc analysis did not demonstrate any differences between the leuprorelin acetate and goserelin arms in either disease specific mortality or the development of distant metastases. However, biochemical failure (an increase in the PSA level of > 2 nanograms per millilitre above the nadir[10]) was significantly higher in the goserelin arm (HR: 0.53; 95% CI: 0.30 to 0.91; p = 0.0236)[1,4,6,9].

2.2 Safety

The data from the post hoc analysis showed that the type and incidence of adverse events were similar for goserelin and leuprorelin acetate[1,10,11]. The Medicines and Healthcare Products Regulatory Agency (MHRA) concluded that the safety of leuprorelin acetate is expected to be similar to, if not better than, the established profile of this class of medicines, since the population remains the same and its use is relatively short-term. The MHRA stated that the benefits of neoadjuvant treatment prior to radiotherapy, in terms of prostate volume reduction, and increased prostate-specific antigen progression free survival and OS are expected to outweigh the risks[4,6].

2.3 Points to note

- The MHRA suggested that comparative data between goserelin and leuprorelin acetate in the neoadjuvant setting would be useful to support the licence extension. The rationale was the goserelin had already been granted an MHRA licence for neoadjuvant use in treating prostate cancer[1].
- There were no trials in the neoadjuvant setting where the outcomes were analysed according to the type of luteinising hormone releasing hormone (LHRH) agonist used, hence the reason for a post hoc analysis[1].
- No outcome differences were reported in OS in Warde et al (2011)[1], whereas, in Jones et al (2011), OS favoured goserelin. The MHRA reported that this was likely to be a chance finding rather than a medicine-related toxicity[4,6].
- The dose of leuprorelin acetate used in the Jones et al (2011) study was higher than the licensed dose of leuprorelin acetate; however, the MHRA commented that it is acceptable to extrapolate data from studies investigating higher doses of leuprorelin acetate. The allocation of patients to goserelin and leuprorelin

acetate was not randomised in this study and there were larger numbers of patients treated with goserelin compared to leuprorelin acetate[4,6].

- The MHRA reported that the reductions in testosterone levels following treatment with leuprorelin acetate were comparable to those patients taking either 3.6 mg per month goserelin or 7.5 mg per month leuprorelin acetate[4,6].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The Welsh Cancer Intelligence and Surveillance Unit Dashboard reported that 2,419 men in Wales were diagnosed with prostate cancer in 2012[12]. The NICE costing statement reports that 73% of patients diagnosed with prostate cancer are considered to be at intermediate or high-risk and are thus eligible for neoadjuvant treatment with a LHRH agonist[13]. Based on this information, it is assumed that approximately 1,766 patients in Wales would be eligible for neoadjuvant treatment with a LHRH agonist. It is also assumed that patients undergoing surgery are likely to be diagnosed with intermediate- and high-risk prostate cancer but are not eligible or prefer not to undergo neoadjuvant LHRH agonist treatment. During 2011–2012, 232 patients in Wales underwent prostatectomy procedures[14]. Taking this into account, it is estimated that there is an annual incidence of 1,534 patients across NHS Wales that would be treated with leuprorelin acetate in the neoadjuvant setting.

Table 1. Incremental budget impact when using leuprorelin acetate as neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients eligible for neoadjuvant treatment with a LHRH agonist	1,534	1,534	1,534	1,534	1,534
Number of patients treated with a LHRH agonist (assuming a 90% treatment rate)	1,381	1,381	1,381	1,381	1,381
Proportion of patients treated with leuprorelin acetate	10%	20%	30%	40%	50%
Number of patients treated with leuprorelin acetate (Prostap® 3 DCS)	138	276	414	552	691
Incremental cost per patient*	−£18.56	−£18.56	−£18.56	−£18.56	−£18.56
Budget impact	**−£2,561**	**−£5,123**	**−£7,684**	**−£10,245**	**−£12,825**

LHRH: luteinising hormone-releasing hormone.

*Relative to goserelin (Zoladex® LA) therapy based on six months of treatment[1].

Costs are based on Electronic Drug Tariff and Monthly Index of Medical Specialities (MIMS) list prices as of 28 July 2014[15,16]; figures are based on medicine acquisition costs only.

Based on the number of patients eligible for treatment with leuprorelin acetate in the neoadjuvant setting, the company anticipates savings of £2,561 in year one and £12,825 in year five.

3.1.1 AWTTC critique

- The budget impact calculations assume all patients would be treated with the three monthly formulation of leuprorelin acetate (Prostap® 3 DCS) which is cost saving compared to the three monthly formulation of goserelin (Zoladex® LA).

The monthly formulation of leuprorelin acetate (Prostap® SR DCS) has an incremental cost per patient of £61.44 compared to the monthly formulation of goserelin (Zoladex®) over six months of treatment. The budget impact is subject to uncertainty as it has not taken into account the use of the monthly preparation of leuprorelin acetate which is more costly than the monthly preparation of goserelin. However, the applicant company state that, in clinical practice, the vast majority of patients would be treated with three monthly formulations of LHRH agonists[1].

- The uptake figures have been estimated by the company and are subject to uncertainty.
- AWTTC are unable to verify the treatment rate of 90% used in the budget impact calculations.

3.2 Comparative unit costs

Table 2 provides an example of the comparative acquisition costs for leuprorelin acetate and goserelin.

Table 2. Examples of acquisition costs for leuprorelin acetate and goserelin as neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

Medicine	Example regimen*	Cost per six months†
Leuprorelin acetate (Prostap® SR DCS) 3.75 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe	3.75 mg subcutaneous or intramuscular injection every month	£451.44
Leuprorelin acetate (Prostap® 3 DCS) 11.25 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe	11.25 mg subcutaneous injection every three months	£451.44
Goserelin (Zoladex®) 3.6 mg implant in a pre-filled syringe	3.6 mg subcutaneous injection every 28 days	£390.00
Goserelin (Zoladex® LA) 10.8 mg implant in a pre-filled syringe	10.8 mg subcutaneous injection every 12 weeks.	£470.00
*Regimen based on the Summary of Product Characteristics (SPC) dosing instructions[2,3,17,18]. †Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of 28 July 2014[15]. This table does not imply therapeutic equivalence of medicines or the stated doses. Refer to the SPCs for full dosing details[2,3,17,18].		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 3 July 2014
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Takeda UK Ltd. Form C: Limited appraisal submission. Leuprorelin acetate (Prostap® SR DCS/Prostap® 3 DCS). 2014.
2 Takeda UK Ltd. Prostap® 3 DCS. Summary of Product Characteristics. May 2014. Available at: http://www.medicines.org.uk/emc/medicine/24680. Accessed Jul 2014.
3 Takeda UK Ltd. Prostap® SR DCS. Summary of Product Characteristics. May 2014. Available at: http://www.medicines.org.uk/emc/medicine/24679. Accessed Jul 2014.
4 Medicines and Healthcare Products Regulatory Agency. UKPAR Prostap® 3 DCS 11.25 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe. PL 16189/0013. Scientific Discussion. Apr 2011. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con120444.pdf. Accessed Jul 2014.
5 Medicines and Healthcare Products Regulatory Agency. Marketing authorisations granted in April 2011. 2011. Available at: http://www.mhra.gov.uk/home/groups/l-reg/documents/licensing/con117529.pdf. Accessed Jul 2014.
6 Medicines and Healthcare Products Regulatory Agency. UKPAR Prostap® SR DCS 3.75 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe. PL 16189/0012. Scientific Discussion. Apr 2011. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con120442.pdf. Accessed Jul 2014.
7 Davis BJ. Prostate volume before and after neoadjuvant cytoreductive androgen suppression and potential predictors of therapeutic efficacy. 2013.
8 Parulekar WR. Statistical analysis report for PR07 patients who received LHRHa (either goserelin or leuprorelin) prior to RT treatment. Nov 2013.
9 Dignam JJ. Comparison of outcomes after neoadjuvant goserelin or leuprorelin for prostate cancer among patients participating in RTOG 9408. Dec 2013.
10 Jones CU, Hunt D, McGowan DG et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *The New England Journal of Medicine* 2011; 365 (2): 107-18.
11 Warde P, Mason M, Ding K et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011; 378: 2104-11.
12 Office for National Statistics. Welsh Cancer Intelligence and Surveillance Unit, April 2014. 2014. Available at: http://www.wcisu.wales.nhs.uk/interactive-cancer-statistics-tool. Accessed Sep 2014.
13 National Institute for Health and Care Excellence. Costing statement: prostate cancer: diagnosis and treatment. Implementing the NICE guideline on prostate cancer (CG175). Jan 2014. Available at: https://www.nice.org.uk/guidance/cg175/resources/cg175-prostate-cancer-costing-statement2. Accessed Jul 2014.
14 NHS Wales Informatics Service. Annual PEDW Data Tables. 2013. Accessed Sep 2014.
15 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2014. Available at: http://www.mims.co.uk/. Accessed Aug 2014.
16 National Health Service Business Services Authority. National Health Service England and Wales. Electronic Drug Tariff. Aug 2014. Available at: http://www.ppa.org.uk/ppa/edt_intro.htm. Accessed Aug 2014.
17 AstraZeneca UK Limited. Zoladex®. Summary of Product Characteristics. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/7855. Accessed Jul 2014.

18 AstraZeneca UK Limited. Zoladex® LA. Summary of Product Characteristics. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/8146. Accessed Jul 2014.