

**5.07 LEUPRORELIN,  
Subcutaneous implant 3.6 mg and 5 mg (as acetate) in  
pre-filled syringe,  
Lerin®  
Sandoz Pty Ltd.**

**1 Purpose of Application**

- 1.1 The submission requested a Section 85, Restricted Benefit listing for leuprorelin subcutaneous (SC) implant (LERIN®) for the treatment of locally advanced and metastatic prostate cancer. Leuprorelin is already listed on the PBS under the brand names Eligard® and Lucrin®, however LERIN SC implant differs to existing PBS-listed brands of leuprorelin in terms of dose and form. This is the first consideration of LERIN by the PBAC.
- 1.2 The basis for the requested listing was as a cost-minimisation versus the existing formulations of leuprorelin; an intramuscular (IM) depot injection (Lucrin® Depot PDS, herein referred to as “Lucrin”) and a SC depot injection (Eligard®). Other gonadotropin-releasing hormone (GnRH) analogues listed on the PBS for locally advanced and metastatic prostate cancer include goserelin SC implant, triptorelin IM depot injection and degarelix SC depot injection. Different formulations across existing GnRH analogues provide for one-, three-, four- and six-monthly dosing frequencies.

**Table 1: Key components of the clinical issue addressed by the submission**

<b>Component</b>	<b>Description</b>
Population	Patients with hormone-dependant prostate carcinoma (locally advanced, Stage C or metastatic, Stage D)
Intervention	One-month formulation: Leuprorelin 3.6 mg SC implant (LERIN), corresponds to “leuprorelin acetate 3.78mg” Three-month formulation: Leuprorelin 5 mg SC implant (LERIN), corresponds to “leuprorelin acetate 5.25mg”
Comparator	One-month formulation: Leuprorelin acetate 7.5 mg IM depot (Lucrin Depot PDS) Three-month formulation: Leuprorelin acetate 22.5 mg IM depot (Lucrin Depot PDS).
Outcomes	Successful testosterone suppression measured by proportion of patients achieving castration level concentrations of $\leq 0.5$ ng/mL.
Clinical claim	LERIN one- and three-month implant are equivalent in terms of comparative effectiveness and safety to Lucrin one- and three-month depot, respectively.

Abbreviations: SC=subcutaneous; IM=intramuscular

Source: Table 1.1, p26 of the submission.

## 2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
LEUPRORELIN 3.6 mg subcutaneous implant, 1 prefilled syringe	1	1	5	\$ [REDACTED]	LERIN® Sandoz Pty Ltd
LEUPRORELIN 5 mg subcutaneous implant, 1 prefilled syringe	1	1	1	\$ [REDACTED]	LERIN® Sandoz Pty Ltd
Category/Program:	General Schedule				
PBS indication:	Locally advanced (Stage 3) and metastatic (Stage 4) prostate cancer				
Restriction:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined				

- 2.1 The Sponsor requested PBS listing for two strengths of LERIN SC implant with different dosing intervals: 3.6 mg administered once a month and 5 mg administered every three months. The requested restriction was consistent with the current PBS listings for other GnRH analogues on the PBS, however, the requested wording differs slightly given that Stage 3 and Stage 4 disease are referred to on the PBS as Stage C and Stage D respectively.
- 2.2 The requested price is [REDACTED] % less (on an AEMP basis) than the current price of existing formulations of leuprorelin, Lucrin and Eligard. The PBAC noted that this was calculated using the current published AEMP for these formulations, which may have been subject to anniversary price reductions and have special pricing arrangements.
- 2.3 If the submission is rejected by the PBAC, it would meet the criteria for an Independent Review.

*For more detail on the PBAC’s view, see section 7 PBAC outcome.*

## 3 Background

### Registration status

- 3.1 The proposed TGA indication is the palliative treatment of patients with advanced hormone-dependent prostate carcinoma. At the time of PBAC consideration, the ACM meeting outcomes were available. The ACM, at its meeting on 4 April 2019, advised that LERIN had an overall positive benefit-risk profile for the proposed indication. The ACM also advised that the proposed indication should be amended to remove the

restriction to ‘hormone-dependent’ carcinomas, as treatment is generally continued in patients with castrate-resistant carcinomas.

## 4 Population and disease

- 4.1 Prostate cancer is the second most common cancer diagnosed in men in Australia, and the third most common cause of cancer death. One in seven men will be diagnosed with prostate cancer by the age of 85. It is more common in older men, with 63% of cases diagnosed in men over 65 years of age.
- 4.2 Clinical guidelines recommend androgen deprivation therapy (ADT) for advanced and metastatic prostate cancer, either by surgical castration or by ongoing treatment with a GnRH analogue. Reducing serum testosterone to castrate levels slows the growth/spread of hormone-dependent prostate cancer.
- 4.3 PBS subsidised GnRH analogues include agonists (leuprorelin, goserelin and triptorelin) and an antagonist (degarelix). Continuous administration of GnRH analogues inhibit the synthesis of gonadotropic hormones, follicle-stimulating hormone (FSH) and luteinising hormone (LH), causing a reduction in serum testosterone. However, GnRH agonists initially cause a surge (also known as a “flare”) in serum testosterone which may cause increased bone pain, bladder obstruction, or other symptoms related to prostate cancer. Anti-androgen drugs are often prescribed concurrently for two to four weeks when commencing therapy with a GnRH agonist to reduce these symptoms<sup>1</sup>. In contrast, GnRH antagonists do not produce the flare phenomenon observed with GnRH agonists.
- 4.4 The submission stated that the recommended doses for leuprorelin depot formulations differ globally, with countries categorised as either ‘high’ or ‘low’ dose markets irrespective of the route of administration (IM or SC). For the one-month and three-month depot formulations, some countries (Japan, New Zealand and all European countries except Spain) registered the minimum effective doses (3.75 mg and 11.25 mg, respectively) whereas other countries (Australia, USA, Canada and Spain) registered higher doses (7.5 mg and 22.5 mg, respectively). The ESC noted that all PBS-listed GnRH analogues are ‘high dose’ formulations by international standards. By comparison, the leuprorelin doses in LERIN are 52% and 78% below the one-month and three-month Lucrin formulations, respectively, and this would represent the first ‘low dose’ preparation available in the Australian market. The ESC considered that the clinical place of a ‘low dose’ formulation in the Australian setting is uncertain. The PBAC noted that this was the first ‘low dose’ formulation in the Australian setting.
- 4.5 The PSCR claimed that LERIN requires no reconstitution or refrigeration and therefore saves clinic time compared to the alternative brands, which must be brought to room

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<sup>1</sup> For the degarelix submission, the PBAC considered 11% of patients requiring co-administered anti-androgens to be a reasonable reflection of clinical practice, (p4, Degarelix Public Summary Document July 2010).

temperature before use. The ESC considered that these claimed advantages would be of minimal importance in the clinical setting.

*For more detail on the PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 For LERIN 3.6 mg (one-month) and 5 mg (three-month) SC implant, the submission nominated Lucrin 7.5 mg (one-month) and 22.5 mg IM depot respectively as the main comparators. The argument provided in support of this nomination was that Lucrin contains the same active ingredient as LERIN and has a larger market share compared to the other available formulation, Eligard.
- 5.2 The ESC considered that Lucrin is an appropriate comparator, however, agreed with the evaluation that LERIN SC implant may also substitute for any of the GnRH analogues listed on the PBS for prostate cancer (i.e. goserelin, triptorelin and degarelix), particularly the corresponding one- and three-month formulations. The ESC noted that goserelin is the current market leader across all GnRH analogues, and both LERIN and goserelin are administered as SC implants. The ESC considered that degarelix was a less relevant comparator as it is not generally used for maintenance treatment. The pre-PBAC reiterated the sponsor's view that Lucrin was the appropriate comparator, noting that Lucrin was listed on a cost-minimisation basis to goserelin, and that use of Lucrin<sup>®</sup> as a comparator allowed for a comparison in the clinical and in the economic analysis that was clear of the influence of weighted pricing (as goserelin also has a gynaecological indication). The PBAC considered that Lucrin was an appropriate comparator, but also that LERIN SC implant may substitute for any of the GnRH analogues listed on the PBS for prostate cancer.
- 5.3 The PBAC recalled that it had recommended all of the currently listed GnRH analogues on the basis of cost-minimisation, and noted that there are now differences in the prices between the drugs, which may be due to differences in anniversary price reductions. At the time of the evaluation, there was limited information about how prices were originally calculated, and therefore it was unclear whether the requested prices for LERIN SC implant were more costly than any of the other GnRH analogues, for the following reasons:
- The AEMP for goserelin 3.6 mg (one-month) implant (\$233.12) is lower than the requested price for LERIN 3.6 mg (one-month) implant (\$██████) and LERIN 5 mg (three-month) implant on a per month basis (\$██████). However, it is unclear whether the AEMP for goserelin 3.6 mg (one-month) implant is a weighted price across multiple indications (prostate cancer, endometriosis, breast cancer, anticipated premature ovarian failure). Goserelin 10.8 mg (three-month) implant, which is only listed for prostate cancer, is more costly on a per month basis.
  - With the exception of goserelin, longer duration GnRH formulations are less costly on a per month basis compared to shorter duration formulations. The AEMP per

month for the six-month formulations of Lucrin and Eligard are [REDACTED] than the requested AEMP per month for LERIN 3.6 mg (one-month) implant (\$267.72 vs \$ [REDACTED]). However, it was unclear whether prices for longer duration formulations included cost offsets associated with fewer administrations.

*For more detail on the PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

6.3 The submission did not provide a direct or indirect comparison between LERIN SC implant and Lucrin IM depot. The submission was based on i) two head-to-head randomised trials comparing LERIN to 'low' dose formulations of leuprorelin acetate not approved in Australia, ii) four single arm studies of LERIN, and iii) one observational 'real-world' study of LERIN as supportive evidence that examined efficacy and tolerability in patients on androgen deprivation therapy (ADT) who switched to LERIN.

6.4 The primary evidence presented for LERIN 3.6 mg (one-month) implant included:

- IMP-3, a randomised trial comparing LERIN 3.6 mg SC implant every four weeks to leuprorelin 7.5 mg SC depot (Enantone® brand) every four weeks, over 16 weeks.
- IMP-4, a single arm study of LERIN 3.6 mg SC implant every four weeks, over 16 weeks.

6.5 The primary evidence presented for LERIN 5 mg (three-month) implant included:

- IMP-8, a randomised trial comparing a single dose of LERIN 5 mg SC implant to a single dose of leuprorelin 11.25 mg SC depot (Trenantone® brand), over 12 weeks.
- IMP-9, a single arm study of a single dose of LERIN 5 mg SC implant, over 12 weeks.
- IMP-12, a single arm study of LERIN 5 mg SC implant every 12 weeks, over 24 weeks

- IMP-13, a single arm study of LERIN 5 mg SC implant every 16 weeks<sup>2</sup>, over 32 weeks.

6.6 The submission stated that irrespective of differences in the route of administration (SC and IM) and dose ('high' vs 'low') between the brands approved in Australia and those used in the trials, the aim of all treatments was to reduce testosterone levels to castrate level. In this respect, the submission argued that all formulations of leuporelin are generally considered to be equally effective, noting the following evidence:

- The PBAC has previously accepted that IM and SC administration can provide equivalent testosterone suppression with the cost-minimisation listing of Eligard (SC injection) to Lucrin (IM injection).
- Akaza 1990<sup>3</sup>: a small randomised trial in Japan demonstrated no difference between one-month 'high' and one-month 'low' dose leuporelin formulations in terms of mean testosterone levels. The trial results indicated mean levels for both formulations were below the nominated castration threshold of 1 ng/mL after 3-4 weeks. The trial did not report the proportion of patients who achieved testosterone suppression  $\leq 0.5$  ng/mL or  $\leq 0.2$  ng/mL.
- Wechsel 1996<sup>4</sup> and Sharifi 2002<sup>5</sup>: two randomised trials demonstrating no difference between one- and three-month 'low' dose formulations and one- and three-month 'high' dose formulations respectively, in terms of achieving successful testosterone suppression. The submission implied these trials provided indirect evidence, in combination with Akaza 1990, of no difference in efficacy for three-month 'high' and three-month 'low' dose formulations.
- TGA Public Assessment Report 2010 for Lucrin 30mg XL SC depot (not registered in Australia)<sup>6</sup>: "whilst there are no data directly comparing the 3-(month) depot formulations of 11.25 mg ['low' dose] and 22.5 mg ['high' dose], indirect comparisons of available clinical data confirm that both formulations are safe and efficacious in the treatment of advanced or metastatic prostate cancer."

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<sup>2</sup> This is not consistent with the draft TGA PI recommended dosing interval of every 12 weeks.

<sup>3</sup> Akaza H, Aso Y, Koiso K, Fuse H, Isurugi K, Okada K, Usami M, Kotake T, Ohashi T, Ueda T, et al. Leuporelin acetate depot: results of a multicentre Japanese trial. TAP-144-SR Study Group. J Int Med Res. 1990;18 Suppl 1:90-102.

<sup>4</sup> Wechsel HW, Zerbib M, Pagano F, Coptcoat MJ. Randomized open labelled comparative study of the efficacy, safety and tolerability of leuporelin acetate 1M and 3M depot in patients with advanced prostatic cancer. Eur Urol. 1996;30 Suppl 1:7-14; discussion 19-21.

<sup>5</sup> Sharifi R, Browneller R; Leuprolide Study Group. Serum testosterone suppression and potential for agonistic stimulation during chronic treatment with monthly and 3-month depot formulations of leuprolide acetate for advanced prostate cancer. J Urol. 2002 Sep;168(3):1001-4.

<sup>6</sup> Details and the source for Study EC404 were not provided in the submission. The evaluation identified the TGA Australian Public Assessment report for leuporelin acetate, September 2010:

<https://www.tga.gov.au/sites/default/files/auspar-lucrin.pdf>

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6.7 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>LERIN 3.6 mg (one-month) formulation</b>		
2002-18-IMP-3 (IMP-3)	Internal study report. Randomized, open label, multicenter, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of Leuprorelin 1M implant HEXAL in patients with advanced prostatic cancer in comparison to Enantone®.  Geiges et al. Clinical development of two innovative pharmaceutical forms of leuprorelin acetate. Therapeutics Advances in Urology. 2013; 5(1): 3-10.	8 June 2004  Ther Adv Urol 2013 5(1) 3–10
2002-19-IMP-4 (IMP-4)	Internal study report. Open label, multicenter, phase II study on pharmacokinetics, pharmacodynamics, efficacy and safety of Leuprorelin 1M implant HEXAL in patients with advanced prostatic cancer.  Geiges et al. Clinical development of two innovative pharmaceutical forms of leuprorelin acetate. Therapeutics Advances in Urology. 2013; 5(1): 3-10.	18 June 2004  Ther Adv Urol (2013) 5(1) 3–10
<b>LERIN 5 mg (three-month formulation)</b>		
2001-22-IMP-8 (IMP-8)	Internal study report. 2001. Laboratory values of di-hydro testosterone (DHT)  Solaric et al. Testosterone suppression with a unique form of leuprorelin acetate as a solid biodegradable implant in patients with advanced prostate cancer: results from four trials and comparison with the traditional leuprorelin acetate microspheres formulation. Therapeutic Advances in Urology 2017, 9(6): 127-136.	21 July 2003  Ther Adv Urol 2017, Vol. 9(6) 127–136
2001-34-IMP-9 (IMP-9)	Internal study report. Open label, multicentre, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of leuprorelin Hexal implant in 30 patients with advanced prostate cancer.  Solaric et al. Testosterone suppression with a unique form of leuprorelin acetate as a solid biodegradable implant in patients with advanced prostate cancer: results from four trials and comparison with the traditional leuprorelin acetate microspheres formulation. Therapeutic Advances in Urology 2017, 9(6): 127-136	21 July 2003  Ther Adv Urol 2017, Vol. 9(6) 127–136
2003-65-IMP-12 (IMP-12)	Internal study report. Multi-center, open label phase III study on the efficacy, tolerability and pharmacokinetics of Leuprorelin 5 mg HEXAL after two subsequent administrations separated by 12 weeks in patients with advanced prostatic cancer over a period of 24 weeks.  Solaric et al. Testosterone suppression with a unique form of leuprorelin acetate as a solid biodegradable implant in patients with advanced prostate cancer: results from four trials and comparison with the traditional leuprorelin acetate microspheres formulation. Therapeutic Advances in Urology 2017, 9(6): 127-136  Geiges et al. Clinical development of two innovative pharmaceutical forms of leuprorelin acetate. Therapeutics Advances in Urology. 2013; 5(1): 3-10.	23 August 2005  Ther Adv Urol 2017, Vol. 9(6) 127–136  Ther Adv Urol (2013) 5(1) 3–10
2003-66-IMP-13 (IMP-13)	Internal study report. Multi-center, open label phase III study on the efficacy, tolerability and pharmacokinetics of Leuprorelin 5 mg implant HEXAL after two subsequent administrations separated by 16 weeks in patients with advanced prostatic cancer over a period 32 weeks.  Solaric et al. Testosterone suppression with a unique form of leuprorelin acetate as a solid biodegradable implant in patients with advanced prostate cancer: results from four	17 August 2005  Ther Adv Urol 2017, Vol. 9(6) 127–136

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Trial ID	Protocol title/ Publication title	Publication citation
	trials and comparison with the traditional leuprorelin acetate microspheres formulation. Therapeutic Advances in Urology 2017, 9(6): 127-136	
<b>Observational study (supportive evidence)</b>		
Gravel et al (2013)	Internal report. Observational Study with Leuprone® HEXAL® 1-Monatsdepot / 3-Monatsdepot in Advanced Hormone-Dependent Prostate Cancer.  Gravel et al. 2013. Two innovative pharmaceutical forms of leuprorelin: Results from 818 patients with advanced prostate cancer. Advanced Therapeutics. 2013; 30(3): 271-85.	13 March 2013  Adv Ther 2013 30(3):271–85.

Source: Table 2.3, p45-46 of the submission.

6.8 The key features of the included trials and studies are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N <sup>a</sup>	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>3.6 mg LERIN (one-month formulation)</b>					
IMP-3	63	R, OL, MC. Phase III PK, PD, efficacy & safety trial of LERIN 3.6 mg vs Enantone 3.75 mg	Low	Advanced prostate cancer	%patients with successful testosterone suppression and with levels ≤0.5 ng/mL until Wk 16
IMP-4	20	Single arm, OL, MC, 16 wks. Phase II PK, PD, efficacy & safety study.	High*	Advanced prostate cancer	
<b>5 mg LERIN (three-month formulation)</b>					
IMP-8	61	R, OL, MC. Phase III PK, PD, efficacy & safety trial of LERIN 5 mg vs Trenantone 11.25 mg	Low	Advanced prostate cancer	%patients with successful testosterone suppression and with levels ≤0.5 ng/mL at Wk 12
IMP-9	33	Single arm, OL, MC, 12 wks. Phase III PK, PD, efficacy & safety study.	High*	Advanced prostate cancer	
IMP-12	18	Single arm, OL, MC, 24 wks. Phase III efficacy, tolerability & PK study.	High*	Advanced prostate cancer	%patients with successful testosterone suppression at Wk 8 & Wk 24
IMP-13	16	Single arm, OL, MC, 32 wks. Phase III efficacy, tolerability & PK study.	High*	Advanced prostate cancer	%patients with successful testosterone suppression at Wk 8 & Wk 32
<b>Observational study (supportive evidence)</b>					
Gravel 2013	818	Prospective observational study to examine the efficacy and tolerability of switching to LERIN from a previous LHRH agonist (leuprorelin, goserelin, buserelin, triptorelin).	High*	Advanced hormone-dependent prostate cancer and pre-treatment with leuprorelin or another LHRH agonist	Serum testosterone and prostate-specific antigen (PSA) levels

<sup>a</sup> The “N” presented in this table refer to the randomised number of patients, i.e. the ITT population.

Abbreviations: LHRH=luteinising hormone-releasing hormone; MC=multi-centre; OL=open label; PD=pharmacodynamics; PK=pharmacokinetics; R=randomised.

\* Bias considered to be high on the basis of the single-arm or observational study design.

Source: compiled during evaluation from CSRs provided with the submission; Gravel et al 2013.

6.9 Overall, the risk of bias in the randomised trials was considered low despite the open-label design, given that the primary endpoint (testosterone levels) was an objective laboratory measure. However, the submission did not comment on the type and precision of the laboratory tests used in the LERIN trials/studies or how this compared

to the Australian setting. “Results of testosterone determinations are dependent on assay methodology [and] it is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions” (Lucrin Product Information [PI]).

- 6.10 The submission did not assess the risk of bias in the single arm and real-world studies, but stated that non-randomised studies are known to increase the risk of bias and single-arm studies reduce the ability to determine the treatment effect. The risk of bias in the real-world study (Gravel 2013) was considered high because complete data was available for only a small proportion of the overall study population. Less than one-third of patients had documented laboratory measurements by Visit 3 (the final visit) and were included in the per protocol efficacy analyses.

### ***Comparative effectiveness***

- 6.11 The key outcomes presented in the submission and relied on in the clinical claim were the proportion of patients who achieved and maintained successful testosterone suppression defined as  $\leq 0.5$  ng/mL. These were dual primary outcomes in all of the trials and single-arm studies presented in the submission, assessed at slightly different time-points.
- 6.12 The PBAC previously based recommendations for the listing of ADT agents on the suppression of serum testosterone concentrations at castrate levels ( $\leq 0.5$  ng/mL). In July 2010, “the PBAC accepted that use of testosterone levels as a surrogate outcome was reasonable” (Degarelix Public Summary Document July 2010). However, the testosterone outcome was defined as the cumulative probability of maintaining testosterone  $\leq 0.5$  ng/mL from Day 28 to Day 364, rather than the absolute frequencies of patients achieving testosterone  $\leq 0.5$  ng/mL at specific points in time. In November 2006, the PBAC recommended the equi-effective doses for triptorelin and goserelin on the basis “equivalence in terms of serum concentrations of testosterone” however the specific outcome relied on was not reported (Triptorelin PSD November 2006). While the ESC acknowledged that testosterone level was an appropriate surrogate outcome measure, it questioned the relevance of this outcome in clinical practice as treated patients do not routinely have testosterone levels monitored.
- 6.13 The submission stated that the treatment guidelines and regulatory agencies define the response to ADT in terms of achieving testosterone levels  $\leq 0.5$  ng/mL. However, the ESC noted that the European Association of Urology (EAU) recommended lowering the threshold of the target castrate level from  $< 0.5$  ng/mL to  $< 0.2$  ng/mL in 2015, following the finding that the mean value of testosterone is 0.15 ng/mL after surgical castration. Failure to reach testosterone levels  $< 0.2$  ng/mL following ADT could correlate with the time to castrate-resistant prostate cancer and mortality. In a

secondary analysis of the PR.7<sup>7</sup> trial, in which 626 evaluable patients received ADT for a median of eight years, there was a significant difference in cause-specific survival among those who had a first-year minimum nadir testosterone of  $\leq 0.2$  ng/mL,  $>0.2$  to  $<0.5$  ng/mL, and  $\geq 0.5$  ng/mL. Patients with their first-year nadir testosterone level consistently  $>0.2$  ng/mL had a significantly higher risk of dying.

- 6.14** The ESC noted that high sensitivity assays were previously unavailable in laboratories to accurately quantify testosterone levels below 0.5 ng/mL, therefore 0.5 ng/mL was used as the threshold, however, modern high sensitive assays are now available to detect much lower testosterone levels, and the suppression of testosterone is associated with increased efficacy. The PBAC noted that: previous PBAC submissions for GnRH analogues have used  $<0.5$  ng/mL as the threshold; the castrate levels of serum testosterone remain at  $<0.5$  ng/mL according to the National Comprehensive Cancer Network 2018; and all the pivotal clinical trials for all available ADT used castrate testosterone levels of  $\leq 0.5$  ng/mL. However, the PBAC considered that a testosterone level of 0.5 ng/mL may be an inadequate outcome measure for comparing the efficacy of high dose and low dose GnRH analogues, in light of the recent recommendations of the European Association of Urology, and results of subgroup analyses of the PR.7 trial, both referred to above.
- 6.15** Table 4 presents the results of the dual primary outcomes in the included trials and single-arm studies in the per protocol (valid case) populations. Trial participants who experienced application failure were excluded from the primary analyses. The proportion of patients with successful testosterone suppression was lower in the ITT analysis compared to the PP analysis as expected.

**Table 4: Results of the primary outcomes across the trials and studies (per protocol / 'valid case' population)**

	One-monthly doses			Three-monthly doses		
	LEU 3.6mg SC implant (LERIN®)	LEU 3.75mg SC depot (Enantone®)	p-value	LEU 5mg SC implant (LERIN®)	LEU 11.25mg SC depot (Trenantone®)	p-value
<b>Patients with testosterone <math>\leq 0.5</math> ng/mL within 8 weeks, n/N (%)</b>						
IMP-3	25/26 (96%)	25/29 (86%)	0.23	-	-	-
IMP-4	20/20 (100%)	-	-	-	-	-
IMP-8	-	-	-	28/29 (97%)	21/26 (81%)	0.09
IMP-12	-	-	-	15/15 (100%)	-	-
IMP-9	-	-	-	29/29 (100%)	-	-
IMP-13	-	-	-	15/15 (100%)	-	-
<b>Patients with testosterone <math>\leq 0.5</math> ng/mL from Week 8 until Week 12, 16, 24 or 32, n/N (%)</b>						
IMP-3 (Wk 16)	22/26 (85%)	23/29 (79%)	0.61	-	-	-
IMP-4 (Wk 16)	20/20 (100%)	-	-	-	-	-
IMP-8 (Wk 12)	-	-	-	28/29 (97%)	21/26 (81%)	0.09
IMP-8 (Wk 16)#	-	-	-	26/29 (90%)	19/26 (73%)	0.12

<sup>7</sup> Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT [published correction appears in J Clin Oncol. 2016 Jun 1;34(16):1965]. *J Clin Oncol*.

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	One-monthly doses			Three-monthly doses		
	LEU 3.6mg SC implant (LERIN®)	LEU 3.75mg SC depot (Enantone®)	p-value	LEU 5mg SC implant (LERIN®)	LEU 11.25mg SC depot (Trenantone®)	p-value
IMP-12 (Wk 12)	-	-	-	14/15 (93%)	-	-
IMP-12 (Wk 24)	-	-	-	14/15 (93%)	-	-
IMP-9 (Wk 12)	-	-	-	29/29 (100%)	-	-
IMP-9 (Wk 16)#	-	-	-	29/29 (100%)	-	-
IMP-13 (Wk 16)#	-	-	-	15/15 (100%)	-	-
IMP-13 (Wk 32)#	-	-	-	15/15 (100%)	-	-

Abbreviations: LEU=leuprorelin; SC=subcutaneous

# Outcome reported at time point beyond recommended 12-week dosing regimen

Source: Tables 1.1.1 and 1.2.2 (p40-41) of CSR IMP-3; Tables 1.1 and 1.2 (p35) of CSR IMP-4; Tables 1.2.5 (p41) and 1.2.6 (p43) of CSR IMP-8; Tables 1.1.5, 1.2.5 and 1.2.6 (p35-37) of CSR IMP-9; Tables 11.8 and 11.9 (p63) of CSR IMP-12; Tables 11.8 and 11.9 (p63) of CSR IMP-13.

6.16 For LERIN 3.6 mg (one-month) SC implant, the results demonstrated:

- Nearly all patients treated with LERIN SC implant successfully reached testosterone suppression at Week 8 (96% in IMP-3 and 100% in IMP-4). There were no significant differences in the proportions of patients achieving the outcome between LERIN SC implant to the 'low' dose Enantone SC depot (96% vs 86% respectively in IMP-3).
- Most patients treated with LERIN SC implant successfully reached and maintained testosterone suppression at Week 8 until Week 16 (85% in IMP-3 and 100% in IMP-4). There were no significant differences in the proportions of patients achieving the outcomes between LERIN SC implant to the 'low' dose Enantone SC depot (85% vs 79% respectively in IMP-3).

6.17 For LERIN 5 mg (three-month) SC implant, the results demonstrated:

- Nearly all patients treated with the LERIN SC implant successfully reached testosterone suppression at Week 8 (97% in IMP-8, 100% in IMP-9, IMP-12 and IMP-13). There were no significant differences in the proportion of patients achieving outcomes between the LERIN SC implant and the 'low' dose Trenantone SC depot (97% vs 81% respectively in IMP-8).
- Most patients treated with the LERIN SC implant successfully reached and maintained testosterone suppression at Week 8 until Week 12 (97% in IMP-8, 100% in IMP-9, and 93% in IMP-12) or Week 24 (100% in IMP-12). There were no significant differences in the proportion of patients achieving the outcome at Week 16 between the LERIN SC implant and the 'low' dose Trenantone SC depot (90% vs 73% respectively in IMP-8).

6.18 Supportive evidence reported by Gravel et al 2013 indicated that the proportion of patients with a serum testosterone of  $\leq 0.5$  ng/mL was similar or increased after patients switched to the LERIN SC implant. The results were consistent for patients who commenced the LERIN 3.6 mg (one-month) or 5 mg (three-month) SC implant,

and in patients pre-treated with the ‘low’ dose leuporelin SC depot or the goserelin SC implant.

- 6.19 A retrospective analysis of IMP-8, IMP-9, IMP-12 and IMP-13 reported in Solarić et al 2017 indicated a much lower proportion of patients in IMP-8 and IMP-9 achieved testosterone suppression  $\leq 0.2$  ng/mL compared to  $\leq 0.5$  ng/mL. Although similar to the proportions treated with Trenantone SC depot, only 48%, 52% and 48% of patients treated with the LERIN 5 mg SC implant had a serum testosterone of  $\leq 0.2$  ng/mL at Weeks 8, 12 and 16 respectively. In IMP-12 and IMP-13, median serum levels of testosterone  $\leq 0.2$  ng/mL were achieved at Week 4 and lasted up to 24 weeks and 32 weeks for the administration interval of 12 and 16 weeks, respectively. At the last value measured (Week 24 and Week 32 for the 12- and 16-week administration interval studies, respectively), median testosterone levels were 0.09 ng/mL in both studies. The ESC noted that the efficacy of LERIN is uncertain using testosterone suppression levels of  $\leq 0.2$  ng/mL compared to  $\leq 0.5$  ng/mL.
- 6.20 Data was extracted during the evaluation from four single-arm studies cited in the Lucrin and Eligard PIs<sup>8</sup>. On the basis of naïve comparison, a similar proportion of patients achieved testosterone levels of  $\leq 0.5$  ng/mL with Lucrin and Eligard compared to the LERIN SC implant in the per protocol population. However, the proportion that achieved testosterone levels of  $\leq 0.2$  ng/mL appeared to favour Lucrin (48% at Week 8 on LERIN versus 98% at Week 6 on Lucrin).

### Comparative harms

- 6.21 A summary of treatment emergent adverse events (TEAEs) from IMP-3, IMP-4, IMP-8 and IMP-9 is presented in Table 5.

**Table 5: Number of TEAEs reported for each patient**

Trial*	Drug	N	Number of patients (%) with respective number of AEs					
			0	1	2	3	4	10
<b>One-monthly dose</b>								
IMP-3	LERIN (LEU 3.6mg)	32 <sup>a</sup>	24 (75)	5 (16)	1 (3)	0	2 (6)	–
	Enantone (LEU 3.75mg)	31	22 (71)	8 (26)	0	1 (3)	0	–
IMP-4	LERIN (LEU 3.6mg)	20	3 (15)	10 (50)	6 (30)	1 (5)	–	–

<sup>8</sup> Sharifi R, Soloway M. Clinical study of leuprolide depot formulation in the treatment of advanced prostate cancer. The Leuprolide Study Group. J Urol. 1990 Jan;143(1):68-71.

Sharifi R, Bruskewitz RC, Gittleman MC, Graham SD Jr, Hudson PB, Stein B. Leuprolide acetate 22.5 mg 12-week depot formulation in the treatment of patients with advanced prostate cancer. Clin Ther. 1996 Jul-Aug;18(4):647-57.

Perez-Marreno R, Chu FM, Gleason D, Loizides E, Wachs B, Tyler RC. A six-month, open-label study assessing a new formulation of leuprolide 7.5 mg for suppression of testosterone in patients with prostate cancer. Clin Ther. 2002 Nov;24(11):1902-14.

Chu FM, Jayson M, Dineen MK, Perez R, Harkaway R, Tyler RC. A clinical study of 22.5 mg. La-2550: A new subcutaneous depot delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol. 2002 Sep;168(3):1199-203.

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Trial*	Drug	N	Number of patients (%) with respective number of AEs					
			0	1	2	3	4	10
<b>Three-monthly doses</b>								
IMP-8	LERIN (LEU 5 mg)	32	18 (56)	9 (28)	3 (9)	1 (3)	1 (3)	–
	Trenantone (LEU 11.25 mg)	28	18 (64)	2 (7)	4 (14)	4 (14)	0	–
IMP-9	LERIN (LEU 5 mg)	32	14 (44)	5(16)	4 (13)	2 (6)	3 (9)	2 (6)

\* Not reported for IMP-12 and IMP-13

<sup>a</sup> 30 patients had been randomised to the LERIN arm, however 2 patients randomised to the Enantone arm received the wrong study medication and were administered LERIN, and were therefore included in the safety analysis for LERIN.

Abbreviations: LEU=leuprorelin

Source: IMP-3 CSR p46, IMP-4 CSR p41, IMP-8 CSR p51, IMP-9 CSR p43

6.22 Patients who had administered the three-monthly doses had three or more TEAEs compared to patients who received the one-monthly doses. The majority of these TEAEs were mild or moderate in severity, and no patients discontinued due to the TEAEs. The most common adverse event were hot flushes. Overall, the safety data reported across the trials and studies were consistent with the established safety profile of leuprorelin. No new safety concerns were identified. The ESC noted that due to the mechanism of action of the treatment, a lack of toxicity may likely imply a lack of treatment efficacy.

### **Clinical claim**

6.23 The submission described the LERIN 3.6 mg (one-month) SC implant as non-inferior to Enantone 3.75mg, and therefore non-inferior to the Lucrin 7.5 mg (one-month) IM depot, and the LERIN 5 mg (three-month) SC implant as non-inferior to Trenantone 11.25 mg, and therefore non-inferior to the Lucrin 22.5 mg (three-month) IM depot.

6.24 The submission did not provide any comparison between the LERIN SC implant and the Lucrin IM depot, did not consider whether application failures may differ between the formulations (which may influence cost-effectiveness), or comment on the assay methodology for measuring testosterone levels in the trials and any potential differences to current practice in Australia. Despite these issues, the clinical claim of successful testosterone suppression at serum levels  $\leq 0.5$  ng/mL was generally supported based on the evidence presented in the submission, given that:

- nearly all (96% to 100%) patients (per protocol analysis) treated with the LERIN 3.6mg or 5mg SC implant in the two trials and four single-arm studies achieved a serum testosterone of  $\leq 0.5$  ng/mL by Week 8;
- there was no difference in the proportion of patients with a testosterone of  $\leq 0.5$  ng/mL in the two trials comparing the LERIN 3.6 mg and 5mg SC implants with the 'low' dose Enantone 3.75 mg (one-month) and Trenantone 11.25 mg (three-month) SC depots respectively;
- there were similar efficacy outcomes for the different forms of leuprorelin, irrespective of the route (IM or SC) or dose ('low' or 'high'), including direct

evidence demonstrating similar mean testosterone levels between the ‘low’ (3.75mg) and ‘high’ (7.5mg) dose one-month formulations of the leuprorelin SC depot; and

- the proportion of real-world patients with a serum testosterone of  $\leq 0.5$  ng/mL was similar or had increased after switching from another GnRH analogue to the LERIN SC implant. This proportion, however, was based on approximately one-third of the patients for whom complete data was available.
- 6.25 The ESC considered that the clinical claim was not adequately supported in terms of testosterone suppression at serum levels  $\leq 0.2$  ng/mL. In a naïve comparison, approximately half of patients treated with LERIN 5 mg SC implant achieved that threshold by Week 8 compared to 97.5% of patients treated with Lucrin 7.5 mg IM depot by Week 6. The PSCR argued there is no international consensus on the use of serum testosterone  $< 0.5$  ng/mL vs  $< 0.2$  ng/mL threshold.
- 6.26 Furthermore, the ESC noted that application failure occurred in 10% of patients in the LERIN arm of trial IMP-3. The ESC considered that this would result in wastage if the application failure was recognised, or would result in treatment failure if the application failure was not detected. The pre-PBAC response noted that only 5 applications failed out of 142 applications across all the phase 2 and phase 3 trials, and that the device has since been modified to prevent these types of application failure. The sponsor also noted that education material has been developed and will be used in the Australian market.
- 6.27 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.28 The PBAC considered that the claim of non-inferior comparative safety was adequately supported by the data, but noted the ESC’s concern that the lack of toxicity could imply a lack of treatment efficacy.

### **Economic analysis**

- 6.29 The submission presented a cost-minimisation analysis over one year between LERIN and Lucrin. The recommended doses were assumed to be equi-effective: LERIN 3.6 mg (one-month) SC implant and Lucrin 7.5 mg (one-month) IM depot; and LERIN 5 mg (three-month) SC implant and Lucrin 22.5 mg (three-month) IM depot. Lucrin and Eligard are listed at the same price on the PBS.
- 6.30 The cost-minimisation analysis included the direct medicine costs only (no other costs or cost-offsets) and the Sponsor offered a ■■■% discount for LERIN SC implant (based on the AEMP), summarised in the table below.

**Table 6: Cost-minimisation analysis presented in the submission**

Component	LERIN*	Lucrin / Eligard
<b>One-month</b>		
AEMP	\$ ■■■	\$298.99

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Component	LERIN*	Lucrin / Eligard
DPMQ	\$ [REDACTED]	\$337.75
Dose duration	28 days	28 days
Administrations per year	[REDACTED]	13.04
Cost per year	\$ [REDACTED]	\$3,900
<b>Three-month</b>		
AEMP	\$ [REDACTED]	\$804.13
DPMQ	\$ [REDACTED]	\$899.89
Dose duration	12 weeks	12 weeks
Administrations per year	4.35	4.35
Cost per year	\$ [REDACTED]	\$3,497

\* Prices include the [REDACTED]% discount offered by the Sponsor for LERIN

Source: Excel workbook "3\_Section3\_CostMin\_LERIN.xlsx" of the submission

6.31 The ESC noted that, if LERIN 3.6 mg (one-month) and 5 mg (three-month) implants were listed at the requested prices, they would be the most expensive GnRH formulations on the PBS on a per milligram basis. The ESC considered that the proposed [REDACTED]% discount compared to the price of Lucrin would not compensate for the risk of decreased efficacy due to lower dose. The PBAC noted that, as stated in the pre-PBAC response, GnRH drugs are priced according to the Therapeutic Relativities determined by the PBAC, which are currently based on treatment duration.

**Drug cost/patient/year:**

6.32 \$ [REDACTED] for LERIN 3.6 mg (one-month) SC implant, assuming [REDACTED] scripts per year; and \$ [REDACTED] for LERIN 5 mg (three-month) SC implant, assuming [REDACTED] scripts per year. These estimates are consistent with the cost-minimisation analysis presented in the submission.

**Estimated PBS usage & financial implications**

6.33 The submission was not considered by DUSC. A market share approach, relying predominately on several separate analyses of the PBS 10% sample data, was used to estimate the financial implications of the proposed listing. The submission provided inadequate detail for the underlying assumptions of the analyses of the PBS 10% sample to adequately appraise their validity.

6.34 The submission assumed that the LERIN one- and three-month implants would i) only displace patients initiating leuprorelin; ii) only displace the Lucrin and Eligard one- and three-month formulations; and iii) have no impact on the overall leuprorelin prescription volumes. This was a simplified approach which did not take into consideration that LERIN one- and three-month implants may also substitute for goserelin, triptorelin, and to some extent, degarelix prescriptions, and that prevalent patients may switch between the different GnRH analogues and/or between their durations of therapy. Similarly, the ESC noted that the submission did not account for wastage as a result of application failures.

- 6.35 The submission reported that the 10% PBS sample data for the most recent 12 months to September 2018 showed that approximately 12.6% and 14.6% of leuprorelin and goserelin patients respectively, had previously been treated with the other agent. The submission also stated that treatment changes from the shortest-acting to the longer-acting formulations of leuprorelin occur in approximately 4-5% of patients. The estimated number of LERIN patients may therefore have been underestimated.
- 6.36 The estimated net financial implications for the proposed listing of LERIN 3.6 mg and 5 mg over the first 6 years are presented in the table below.

**Table 7: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Incident patients on leuprorelin (any brand)	■	■	■	■	■	■
<b>LERIN</b>						
Patients initiating LERIN						
1-month	■	■	■	■	■	■
3-month					■	■
Patients continuing LERIN						
1-month	0	■	■	■	■	■
3-month	0					
Total patients on LERIN	■	■	■	■	■	■
Total script of LERIN	■	■	■	■	■	■
Net PBS/RPBS cost <sup>a</sup>	■	■	■	■	■	■
<b>Drugs displaced</b>						
Total script numbers	■	■	■	■	■	■
Net PBS/RPBS cost	■	■	■	■	■	■
<b>Net financial impact</b>						
	■	■	■	■	■	■

<sup>a</sup> Differs from the net PBS/RPBS from Table 4.19, p125 of the submission, as the submission erroneously maintained the patient co-payments for LERIN (PBS) Years 1 – 6.

Source: constructed during the evaluation based on the Section 4 workbook “4\_Attachment 8 Utilisation and Financial Estimates.xlsx” accompanying the submission.

The redacted table shows that at year 6, the estimated number of patients and scrips was be less than 10,000, and the net PBS/PRPBS cost was be less than \$10 million.

- 6.37 Based on the ■% discount offered for the LERIN 3.6 mg (one-month) and 5 mg (three-month) SC implants, and the current prices of Lucrin and Eligard, the submission estimated that the PBS listing of LERIN would result in savings of \$1.79 million over six years.
- 6.38 As acknowledged by the submission, there is conflicting information with regards to what the potential flow-on impact may be to the government budget as a result of the ■% AEMP discount offered for LERIN. The most conservative estimate for the net financial impact on the PBS/RPBS remains as presented in Table 7 above.
- 6.39 At year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million. At year 1, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

For more detail on the PBAC's view, see section 7 PBAC outcome.

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the Section 85, Restricted Benefit listing of the low dose GnRH analogue leuprorelin subcutaneous implant (LERIN) for the treatment of locally advanced and metastatic prostate cancer on the basis of an uncertain clinical need and an uncertain effectiveness compared with PBS-listed high dose GnRH analogues, and potential quality use of medicines issues.
- 7.2 The PBAC noted that there are already several PBS-listed high-dose GnRH analogues indicated for prostate cancer, and that LERIN would therefore not be addressing a significant unmet clinical need.
- 7.3 The PBAC noted that no direct or indirect comparisons between LERIN SC implant and Lucrin IM depot were provided with the submission. The PBAC considered that the data was not sufficient to conclude that LERIN had non-inferior effectiveness in suppressing testosterone compared to the other PBS-listed GnRH analogues.
- 7.4 The PBAC noted that LERIN has different dosing and treatment durations compared to the nominated comparator and other PBS-listed alternatives, and considered that this could be confusing to prescribers, and therefore constituted a potential quality use of medicines issue.
- 7.5 This submission meets the criteria for an Independent Review.

### Outcome:

Rejected

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 9 Sponsor's Comment

The sponsor had no comment.