

5.16 LEUPRORELIN ACETATE

45 mg injection: modified release [1 x 45 mg syringe] (&) inert substance diluent [1 x 2 mL syringe]

Lucrin Depot 6 month PDS[®], AbbVie Pty Ltd

1 Purpose of Application

- 1.1 The minor submission sought the listing of an additional strength of leuprorelin acetate modified release to be administered via intramuscular injection for the treatment of locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.

2 Requested listing

- 2.1 The submission requested the listing of the 45 mg strength of leuprorelin acetate intramuscular formulation. The submission requested the same restriction for the new strength as for the currently listed strengths of the intramuscular formulation: 7.5 mg, 22.5 mg and 30 mg.

For more detail on PBAC's view, see section 6 "PBAC outcome"

3 Background

- 3.1 Leuprorelin is currently listed on the PBS for the treatment of locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate in two forms: a subcutaneous injection and an intramuscular injection. There are four strengths listed for the subcutaneous injection: 7.5 mg, 22.5 mg, 30 mg and 45 mg. There are three strengths listed for the intramuscular injection: 7.5 mg, 22.5 mg and 30 mg.

- 3.2 The requested 45 mg strength of leuprorelin (intramuscular injection) was TGA registered on 5 May 2015 for the palliative treatment of metastatic or locally advanced prostate cancer.

- 3.3 The 45 mg strength has not previously been considered by PBAC.

4 Clinical place for the proposed therapy

- 4.1 The submission claimed that the introduction of the 45 mg strength would provide 6 months (24 weeks) of treatment and that it would allow for greater time between doses. The submission also claimed that this would better align with the expected interval between clinical consultations.

- 4.2 The submission also argued that the new strength would provide patient and clinician choice in the route of administration (intramuscular or subcutaneous).

For more detail on PBAC's view, see section 6 "PBAC outcome"

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

5.3 The submission highlighted that the TGA registration was supported by an open label study (Spitz, 2012), which assessed the safety, efficacy and pharmacokinetics of leuprorelin acetate 45 mg over 48 weeks in men with prostate cancer.

5.4 The primary efficacy endpoint in the study was suppression of serum testosterone to, and maintenance at, medically castrate levels (≤ 50 ng/dL). The submission claimed that this was a well-established surrogate outcome measure in the prostate cancer treatment setting.

5.5 According to the submission, the study demonstrated that testosterone suppression to and below castration levels was rapid and sustained throughout the 48 week treatment period, where 93.7% of subjects had castrate levels of testosterone from week 4 through to week 48.

5.6 During evaluation for registration, the TGA delegate commented that "the failure to achieve testosterone suppression in 6.3% [of subjects] is of concern, given the implications of incomplete control [in the context of] medications that require concomitant castrate levels for their efficacy (eg androgen receptor inhibitors)."

Comparative effectiveness

5.7 The submission asserted that the results were similar to those observed for the 3-month (12 weeks) and 4-month (16 weeks) strengths.

Comparative harms

5.8 The submission asserted that the 6-monthly injection was well tolerated with a safety profile consistent with the current PBS listed strengths of the intramuscular formulation.

5.9 The approved Product Information (PI) for intramuscular leuprorelin 45 mg states that "In a clinical trial of Lucrin Depot 7.5 mg Injection and in two clinical trials with Lucrin Depot 3 Month 22.5 mg Injection and the abovementioned clinical trials with Lucrin Depot 4-Month 30mg Injection and Lucrin Depot 6-Month 45mg injection, reactions were reported to have a possible or probable relationship to drug as ascribed by the

treating physician in 5% or more of the patients receiving the drug. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded”.

Drug cost/patient/year: \$4,248.64

- 5.10 The proposed price ex-manufacturer price for the 45 mg intramuscular formulation is \$1,977.62. The submission has assumed that patients will require two injections per year. This price is the same as that of the 6 month subcutaneous injection.

Table 1: Pricing of currently listed leuprorelin formulations

Leuprorelin acetate strength and formulation (subcutaneous or intramuscular)	Ex-manufacturer price
1 month – subcutaneous	\$368.10
7.5 mg – intramuscular	\$368.10
3 month (22.5 mg)– subcutaneous	\$990.00
3 month (22.5 mg) - intramuscular	\$990.00
4 month (30 mg)- subcutaneous	\$1,319.40
4 month (30 mg) – intramuscular	\$1,319.40
6 month (45 mg) – subcutaneous	\$1,977.62
6 month (45 mg) – intramuscular	Proposed price: \$1,977.62

Estimated PBS usage & financial implications

- 5.11 The submission anticipated that the new strength of the intramuscular formulation will substitute for the alternative PBS listed 6 month subcutaneous formulation of leuprorelin acetate as it offers an alternative route of administration. The submission estimated that this substitution will be cost neutral.
- 5.12 The submission also anticipated that substitution of the new formulation for the 3 and 4 month intramuscular formulations will occur due to the convenience of a 6 monthly dosing regimen. The submission estimated that this substitution will result in a small net saving to the PBS through a predicted reduction in the number of dispensings.
- 5.13 The minor submission estimated a net save to the PBS of less than \$10 million per year in Year 5 of listing, with a total net save to the PBS of less than \$10 million per year over the first five years of listing. This is summarised in the table below as well as the expected patient/prescription numbers.

Table 2: Financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient numbers, pack numbers, and cost of leuprorelin 6 month (intramuscular)					
Number of patients	█	█	█	█	█
Number of packs	█	█	█	█	█
Net cost to PBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Total net cost	\$ █	\$ █	\$ █	\$ █	\$ █
Substitution from leuprorelin acetate 3 and 4 month (intramuscular formulation) and leuprorelin acetate 6 month (subcutaneous formulation)					
Net saving to PBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net saving to RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Total net saving	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to the PBS/RPBS					
Net cost to PBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Total net cost to PBS/RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

The redacted table above shows that at year 5, the estimated number of packs was less than 10,000 and the net save to the PBS/RPBS would be less than \$10 million per year.

For more detail on PBAC's view, see section 6 "PBAC outcome"

6 PBAC Outcome

- 6.1 The PBAC recommended listing the additional strength (45 mg) of intramuscularly administered leuprorelin for the treatment of locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.
- 6.2 The PBAC accepted that there was a clinical place for the additional strength and accepted that the effectiveness of the 6-month formulation was acceptably similar to the 3- and 4-month formulations.
- 6.3 The PBAC noted in the PI for the 6-month intramuscular formulation that in the clinical trials with the 3- and 4-month formulations, possible or probable treatment related reactions occurred in around 5% of patients. The PBAC considered, however, that the adverse events profile remained acceptable.
- 6.4 The PBAC accepted the financial estimates presented and noted that listing the 45 mg intramuscular formulation would result in savings to the PBS.
- 6.5 **Advice to the Minister under subsection 101(3BA) of the Act**

In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that, on the basis of the material available to it, leuprorelin should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal formulation(s).

- 6.6 The PBAC advised that leuprorelin is not suitable for prescribing by nurse practitioners.
- 6.7 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 6.8 The PBAC noted that the existing leuprorelin restrictions do not comply with electronic media requirements and that the implementation of the newest leuprorelin restriction should also include remodelling of the existing restrictions.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
LEUPRORELIN 45 mg injection: modified release [1 x 45 mg syringe] (& inert substance diluent [1 x 2 mL syringe], 1	1	1	Lucrin Depot 6- AbbVie month
Category / Program	GENERAL – General Schedule (Code GE)		
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
Severity:	Locally advanced (stage C) or metastatic (stage D)		
Condition:	Carcinoma of the prostate.		
PBS Indication:	Locally advanced (stage C) or metastatic (stage D) carcinoma of the prostate.		
Restriction Level / Method:	<input 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 checked="" type="checkbox"/> Streamlined		

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

AbbVie welcomes the PBAC decision to recommend this PBS listing to facilitate treatment of patients with leuprorelin every 6 months for carcinoma of the prostate.