6.7 LEUPRORELIN
30 mg injection: modified release [1 x 30 mg syringe] (&) inert substance diluent [1 x 2 ml syringe], 1 pack; Lucrin Depot Paediatric®; AbbVie Pty Ltd.

1 Purpose of Application

1.1 Authority Required listing for leuprorelin for treatment of central precocious puberty (CPP).

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LEUPRORELIN (AS ACETATE): modified release [1 syringe] (&) inert substance diluent [1 syringe], 30mg	1	1	Lucrin® Depot Paediatric	VE

Category / Program	General Schedule
Condition:	~~Treatment of~~ *C*entral *P*recocious *P*uberty ~~(CPP) by or in conjunction with a paediatric endocrinologist or an endocrinologist specialising in paediatrics.~~
PBS Indication:	Central Precocious Puberty
Restriction:	Authority required
Treatment criteria:	*Must be treated by a paediatric endocrinologist; OR* *Must be treated by an endocrinologist specialising in paediatrics*

2.2 The submission seeks listing on the basis of a cost-utility analysis versus no active treatment.

2.3 The ESC considered the restriction should specify that a patient must have progressive CPP for consistency with the clinical management algorithm. Children who present early with rapid progression are most likely to benefit from treatment compared to children with slowly progressive CPP whose adult height (which is the main treatment outcome) is unlikely to be compromised. The Pre-PBAC response noted that in practice, only progressive CPP patients would be treated to ensure that only those patients who will gain a clinical benefit receive therapy.

2.4 The Pre-Sub-Committee Response (PSCR, p3) considered a telephone authority would be a practical approach to listing in order to minimise leakage.

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

3 Background

3.1 **TGA status:** In December 2012, the TGA designated leuprorelin as an orphan drug for the treatment of CPP. The submission was made under TGA/PBAC Parallel Process. The Clinical Evaluation Report stated that the risk-benefit balance for leuprorelin is considered favourable. The Delegate's Overview obtained input from two paediatric endocrinologists regarding the use of leuprorelin in the treatment of CPP in Australia. Leuprorelin was approved for registration in October 2014 for the treatment of children with CPP.

3.2 Leuprorelin is currently listed on the PBS for treatment of locally advanced or metastatic prostate cancer.

3.3 This was the first consideration by the PBAC of leuprorelin for the treatment of CPP.

3.4 The ESC noted that a comprehensive review of current treatment in Australia of central precocious puberty and existing usage of leuprorelin and similar products was not provided in the submission. The ESC recommended that clinical advice from the Endocrine Society of Australia (ESA) be obtained regarding common doses used in clinical practice, current patient numbers, average age at initiation and clinical assessment of primary treatment outcomes. The ESC considered that this would confirm the clinical data provided in the submission as well as support the economic evaluation and financial estimates.

4 Clinical place for the proposed therapy

4.1 Children with CPP have secondary sex characteristics that appear before the age of 8 years in girls and 9 years in boys. The ESC noted that these age groups are chosen to be 2.5 to 3 standard deviations below the mean age of puberty onset (10.5 years for girls and 11.5 years for boys). Early development of sexual characteristics can result in psychosocial problems during puberty, and a reduction in final adult height post-puberty.

4.2 Leuprorelin is proposed as a first-line treatment for children with progressive disease.

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

5 Comparator

5.1 No active treatment/standard of care. Although this is an appropriate comparator, the current standard of care is off-label treatment with a gonadotropin releasing hormone analogue (GnRHa) through the hospital or private system. While the cost-effectiveness of agents such as goserelin, degarelix and triptorelin for the treatment of CPP has not been determined, their current use in the hospital system would result in the costs of treatment being available and therefore an economic comparison would be viable. The ESC considered that off-label use of GnRHas is an appropriate comparator as it is more likely to be replaced in practice than no active treatment/standard of care.

5.2 The Pre-PBAC Response argued that there are no published studies for the use of other GnRHas in CPP and therefore an indirect analysis of these products is not possible as there is no evidence that these off-label products are effective.

For more detail on 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 and welcomed the input from two organisations via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with leuprorelin including halting the progression of CPP, improving final adult height potential, normalising tempo of puberty and associated psychological benefits. The comments highlighted the clinical need for, and current issues of patient access to, this medicine for CPP.

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

Clinical trials

6.3 The submission was based on one head-to-head trial comparing leuprorelin 30mg to leuprorelin 11.25mg (n=84), and an extension study (n=72).

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

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
L-CP07-167	A Phase 3, randomized, multi-centre, open-label study to evaluate the efficacy and safety of Leuprolide Acetate 11.25mg and 30mg formulations in children with central precocious puberty. Abbott Endocrine Inc (Abbott). Clinical Study Report R&D/09/854. 26 March 2012. Lee P et al. Efficacy and safety of leuprolide acetate 3-month depot 11.25mg or 30mg for the treatment of central precocious puberty.	 *Endocrinol Metab* 2012; 97 (5):1572-80
L-CP07-177	A 12 month, multi-centre, open-label extension study to evaluate the safety of leuprolide acetate 11.25mg and 30mg formulations in children with central precocious puberty. Abbott Endocrine Inc (Abbott). Final Clinical Study Report R&D/13/001. 16 May 2013.	

Source: Table B.2:5, p 26 of the submission

6.5 The ESC noted that in CPP, there is a 9:1 ratio of girls to boys affected by the condition. This is adequately reflected in trial populations.

6.6 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Leuprorelin 30mg versus leuprorelin 11.25mg						
L-CP07-167	84	R, OL 6 mths plus 12 week follow-up	Low	Treatment naïve and untreated	Suppression of LH to <4 mIU/mL	Used in C/E analysis
L-CP07-177	72	R, OL 36 mths, plus 12 week follow-up	High	Patients from L-CP07-167	Suppression of the physical signs of puberty	Used

OL=open label; R=randomised; C/E = cost-effectiveness; LH = luteinizing hormone; mths = months
Source: compiled during the evaluation

6.7 Suppression of peak stimulated luteinizing hormone (LH) was the primary outcome in trial L-CP07-167, and this measure was used in the trial based cost-effectiveness analysis of leuprorelin 30mg versus leuprorelin 11.25mg. The proportion of patients who had suppression of the physical signs of puberty in extension study L-CP07-177 was used in the cost-utility analysis. The Pre-PBAC Response reiterated that peak stimulated LH was a valid surrogate measure for efficacy as this is the most commonly used biomarker for the clinical assessment of CPP.

6.8 The submission did not provide a comprehensive collection of evidence regarding the treatment of CPP with GnRHas. Two trials (Badaru et al. 2006 and Fuld et al. 2011) were identified by the ESC that assess the efficacy of lower doses of leuprorelin. The Pre-PBAC Response considered these trials to be of low quality, therefore making them difficult to interpret and in turn uninformative for PBAC decision-making. The design of these trials and their outcomes are summarised in the following table.

Key features of the additional lower dose trials identified by ESC

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Badaru 2006	30	OL 12-month trial of 3.75mg or 7.5mg leuprorelin every month versus 11.25mg leuprorelin depot every 3-months*	High	CPP: treatment naïve and patients previously treated with depot leuprorelin	Stimulated LH; FSH, oestradiol; growth velocity
Fuld 2011	54	OL, R, 2-year trial of 7.5mg leuprorelin monthly or 11.25mg 3-monthly; later the 7.5mg monthly dose changed to 11.5mg 3-monthly and a new 22.5mg 3-monthly treatment arm was added	High	CPP; treatment naïve patients	Stimulated LH, FSH, oestradiol, growth velocity, bone age advancement, weight change, PAH

OL=open label; R=randomised; LH=luteinizing hormone; FSH=follicle stimulating hormone; CPP=central precocious puberty; PAH=predicted adult height. Note: * All patients received the 7.5mg dose every month for the first 24 weeks of the study. Depending on LH levels, patients went on to receive either 3.75mg every month or continued on the 7.5mg dose. Patients whose levels of LH were above 4.5IU/L at week 40 went onto the higher 11.25mg 3-monthly dose.
Source: Badaru 2006; Fuld 2011

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

Comparative effectiveness

6.9 There were more patients in the 30mg treatment group than the 11.25mg treatment group who achieved suppression of peak stimulated LH levels in trial L-CP07-167. The submission suggests that based on this observation, leuprorelin 30mg would be statistically significantly better than no active treatment in suppressing LH levels.

Results of suppression of LH* across the direct randomised trials

Trial ID	Evaluation point for LH suppression	LP 30mg n/N (%)	LP 11.25mg n/N (%)	LP 22.5mg n/N (%)	Risk difference (95% CI)	
L-CP07-167	Month 2 – 6	[redacted]	[redacted]	[redacted]	LP 30mg vs. LP 11.25mg	[redacted]
L-CP07-177	At final visit	36/36 (100%)	31/33 (93.9%)			
Fuld 2011	*During year 1*	*NR*	*14/21 (66.7%)*	*12/13 (92.3%)*	*LP 22.5mg vs. LP 11.25mg*	*0.26 (0.01, 0.51)*
	During year 2		*18/21 (85.7%)*	*13/13 (100%)*		*0.14 (-0.04, 0.32)*

Abbreviations: CI, confidence interval, LH, luteinizing hormone, LP=leuprorelin; NR=not reported
Note: *Defined as Peak-stimulated LH <4 mIU/mL from Month 2 through Month 6
n/N determined from [redacted]
Calculations were made using the life table method adapted from (Koch, McCanless et al (1984)), with incremental LH suppression rate calculated at Months 2, 3, and 6. Only cumulative LH suppression rate at the end of Month 6 is shown in this table
Source: CSR L-CP07-167 p 145 and CSR L-CP07-177 p 145, Fuld 2011, p983-984

6.10 The results of additional studies identified by the ESC are shown in the following table.

Results from the additional lower dose trials

Trial	Leuprorelin 3.75mg monthly	Leuprorelin 11.25mg 3-monthly	Leuprorelin 7.5mg monthly	Leuprorelin 22.5mg 3-monthly	p-value
Mean stimulated peak LH levels (IU/L)					
Badaru 2006	1.73	2.13	1.30	NA	7.5mg vs 3.75mg: 0.019 7.5mg vs 11.25mg: 0.004 3.75mg vs 11.25mg: 0.08
Fuld 2011 Year 1 results	NA	2.52	1.56	1.63	7.5mg vs 11.25mg: <0.001 7.5mg vs 22.5mg: not significant 11.25mg vs 22.5mg: <0.001
Fuld 2011 Year 2 results	NA	2.11	NA	1.63	11.25mg vs 22.5mg: 0.03

FSH= follicle stimulating hormone; LH=luteinizing hormone; vs=versus; NA=not applicable
Source: Badaru 2006; Fuld 2011

6.11 The results from both additional trials show that the 7.5mg monthly, 11.25mg 3-monthly and 22.5mg 3-monthly dosing regimens all reduce mean peak stimulated levels of LH. The monthly dosing with leuprorelin 7.5mg reduced mean levels by a greater amount than 3-monthly dosing with 11.25mg in both trials. The Fuld 2011 trial showed that the higher dose of 22.5mg of leuprorelin resulted in greater suppression of LH than the 11.25mg dose, and similar suppression of LH to the 7.5mg monthly dosing regimen, although the authors state that their study was 'insufficiently

powered to determine the difference at each study visit' (Fuld 2011, p 986). While the Fuld 2011 paper states that there were more patients in the 11.25mg treatment group who had a level of LH of more than 4 IU/L during the trial (almost one third of patients), they state that LH levels decreased over time, and that starting on the 11.25mg dose is sufficient in most cases with a dose increase if persistent hormonal or clinical criteria indicate that this is necessary.

6.12 The ESC considered peak stimulated LH levels are a surrogate measure for efficacy. The stabilisation of Tanner stages, and eventually achieving a normal adult height, are the main aims of treatment. The exact relationship between lower levels of LH and suppression of the physical signs of puberty is not entirely clear, although it appears that consistently reduced levels of LH are necessary for puberty to be suppressed. Advice from the ESA noted that primary treatment outcomes regularly assessed by clinicians when treating children with CPP include the suppression of menstruation and/or arrest or regression of secondary sexual development, return of growth velocity to normal, and suppression of gonadotrophins and oestradiol/testosterone.

6.13 The degree to which the physical signs of puberty are suppressed (the outcome from the extension study used in the modelled evaluation) is shown in the following table. The physical signs of puberty were suppressed in [redacted] of females and in [redacted] of males. The results indicate that both doses of leuprorelin suppress the physical signs of puberty, with a trend [redacted]. The Pre-PBAC Response considered it inappropriate for this claim to be made, highlighting that the trial was not powered to show a difference in this endpoint.

Results of suppression of the physical signs of puberty across the direct randomised trials

Trial ID	Leuprorelin 30mg n with event/N (%) [95% CI]	Leuprorelin 11.25mg n with event/N (%) [95% CI]	Risk difference (95% CI)
L-CP07-167	Females [redacted] Males [redacted]	Females [redacted] Males [redacted]	[redacted]
L-CP07-177	Females [redacted] Males [redacted]	Females [redacted] Males [redacted]	[redacted]

Note: Results exclude patients who entered the study with pubertal staging 5
Source: Table B.6:2, p 47 of the submission and Table 28, p 159-160 of CSR L-CP07-177

6.14 No differences were seen in sex steroid suppression or other clinical measures in Badaru 2006. In Fuld 2011, bone age advancement and growth velocity were similarly suppressed in all treatment groups: mean oestradiol levels and the change in predicted adult height were also similar across the treatment groups.

6.15 While the submission only requested listing of the 30mg 3-monthly dose of leuprorelin, the ESC considered it might be appropriate to consider a lower dose of leuprorelin for listing. The Fuld 2011 trial showed that doses of leuprorelin of 11.25mg and 22.5mg every 3 months result in 'prompt and effective suppression of puberty', with both of these doses reducing stimulated LH and serum oestradiol concentrations by about 10-fold. Bone age advancement and growth velocity were also comparably suppressed. These results are in line with those from trial L-CP07-

167 and the extension study, which showed that in the extension study both the 11.25mg and the 30mg 3-monthly preparations were similarly effective in suppressing peak stimulated LH, and that the lower dose was at least as effective as the 30mg dose in suppressing the physical signs of puberty (with a trend towards greater efficacy). Advice from the ESA confirmed that in current practice in Australia, the dose of leuprorelin used to treat CPP is usually 7.5mg monthly or 22.5mg every three months.

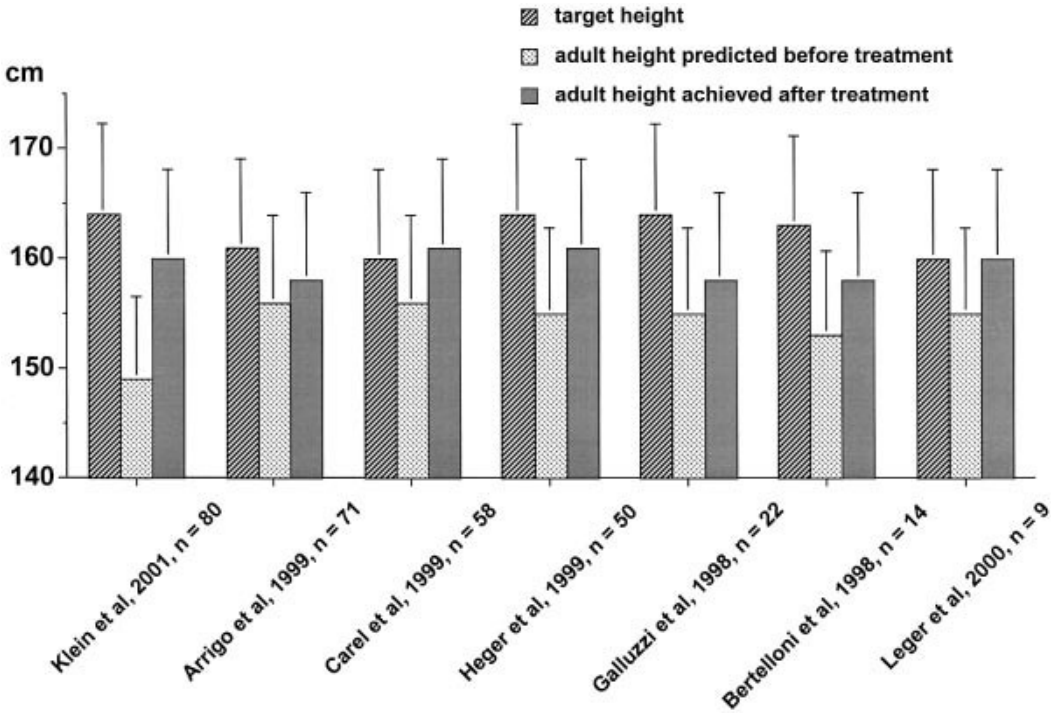
Additional information on the impact of GnRHas on final adult height

6.16 The ESC considered achieving normal adult height to be a primary aim of treatment, with height prediction based on bone age, height and height velocity often being a clinical consideration in deciding to treat.

6.17 Carel (2004) presented results of adult height predicted before treatment and adult height achieved after treatment, from seven studies in patients with CPP (see following Figure). In these studies, the difference in height for treated patients ranged from a height gain of 2.9cm to 9.8cm, compared with untreated patients. Patients who were treated had mean adult heights that ranged from 7cm below to 1cm above their target adult height. These results support the results presented in the submission: for patients who don't receive treatment, expected height will be 6.4cm below target height and for patients who receive leuprorelin, expected height will be 1.3cm below target height (Neely et al (2010) and Lee et al (2011)).

6.18 In one of the seven studies in Carel (2004), Klein (2001), the mean adult height achieved after treatment with deslorelin or histrelin was 159.8cm in girls and 171.1cm in boys with GnRH-dependent precocious puberty. This was a gain over pre-treatment predicted gain of 10.5cm for girls (159.8-149.3cm) and 9.9cm for boys (171.1-161.2cm). The ESC considered that the Klein (2001) data should be used to inform the effects of early treatment and the restriction in order to identify patients with progressive disease to target treatment to those who will gain greatest benefit.

Adult height in girls treated with GnRH analogues for precocious puberty: results of selected studies



Source: Carel 2004

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

Comparative harms

6.19 The trial data showed that injection site reactions were the most common adverse event, reported in up to [redacted] of patients. Other adverse events in the trials were generally mild to moderate and transient. Post-marketing data indicates that bone mineral density can decrease during therapy but that peak bone mass in late adolescence doesn't appear to be affected.

Benefits/harms

6.20 It was not possible to determine the degree of benefit and harms of leuprorelin compared to no active treatment as there are no comparative data. The ESC noted ethical issues surrounding patients receiving no treatment and considered it appropriate for leuprorelin 30mg to be compared to a lower dose in place of no active treatment. This is also reflective of clinical practice whereby all patients are likely to be currently treated with off-label GnRHas.

6.21 A summary of the comparative benefits and harms for leuprorelin 30mg versus leuprorelin 11.25mg is presented in the table below.

Summary of comparative benefits and harms for leuprorelin 30mg vs. leuprorelin 11.25mg

Trial	Leuprorelin 30mg	Leuprorelin 11.25mg	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Leuprorelin 30mg	Leuprorelin 11.25mg	
Benefits						
Proportion of patients with LH <4mIU/mL						
L-CP07-167	[redacted]					
Proportion of patients who have suppression of puberty						
	Leuprorelin 30mg		**Leuprorelin 11.25mg**			**Mean difference*: Leuprorelin 30mg vs. leuprorelin 11.25mg (95% CI)**
	n	**Proportion of patients who have suppression of puberty (95% CI)**	**n**	**Proportion of patients who have suppression puberty (95% CI)**		
L-CP07-177	[redacted]	Females [redacted] Males [redacted]	[redacted]	Females [redacted] Males [redacted]		Females [redacted] Males [redacted]
Harms						
	Leuprorelin 30mg	**Leuprorelin 11.25mg**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Leuprorelin 30mg	**Leuprorelin 11.25mg**	
Injection site reactions						
L-CP07-167	[redacted]					
L-CP07-177	[redacted]					
Headache						
L-CP07-167	[redacted]					
L-CP07-177	[redacted]					
Upper respiratory tract infection						
L-CP07-167	[redacted]					
L-CP07-177	[redacted]					

* Maximum duration of follow-up: L-CP07-167 = 9 months; L-CP07-177 = 45 months

Abbreviations: RD = risk difference; RR = risk ratio; LH = luteinizing hormone; NR = not reported

Source: Compiled during the evaluation/Table B.6:1, p 46 and Table B.6:6, p 51 of the submission

6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with leuprorelin 30mg in comparison to leuprorelin 11.25mg;

- Approximately 17 additional patients would have levels of peak stimulated LH suppressed to less than 4 mIU/mL over a mean duration of exposure of 6 months.
- Approximately 13 fewer patients would have suppression of the physical signs of puberty over a maximum duration of exposure of 42 months, based on a female to male ratio of 9:1.
- Approximately 6 to 7 additional patients would experience injection site reactions, 12 to 17 additional patients would experience headache, and up to 13 fewer patients would experience upper respiratory tract infections in the first 6 to 42 months of exposure.

6.23 The ESC noted that despite a higher dose of leuprorelin having a greater effect in terms of suppression of hormones, the lower dose appears to be superior in terms of suppression of physical signs of puberty, which may be more patient-relevant. It is therefore unclear why only the 30mg strength is being considered for listing. The ESC considered this dose restriction to be of concern as it could restrict current clinical practice. The Pre-PBAC Response considered that treatment with the 11.25mg strength would provide a lower suppression of LH and should not be

recommended as it is not TGA approved or in line with current clinical practice and expert clinical advice.

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

Clinical claim

6.24 The submission claimed that leuprorelin is a safe and effective treatment for patients with CPP. In relation to safety, the evidence supported this claim. In relation to effectiveness, leuprorelin 30mg suppresses peak stimulated LH levels in a greater proportion of patients than leuprorelin 11.25mg. The degree to which leuprorelin 30mg suppresses the physical signs of puberty compared to no active treatment could not be determined from the clinical data. The submission suggested that 'no active treatment' would not suppress the physical signs of puberty.

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

Economic analysis

6.25 The submission presented a trial based cost-effectiveness analysis of leuprorelin 30mg versus leuprorelin 11.25mg and a modelled cost-utility analysis of leuprorelin 30mg versus no active treatment.

Summary of cost-utility model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 3.5 years in the trial
Outcomes	Quality adjusted life years
Methods used to generate results	The submission states it is a Markov model with 6 health states, but it is more reflective of a decision tree analysis with a self-absorbing death state
Utilities	Time trade-off study

Source: compiled during the evaluation

6.26 The PSCR reiterated that a 20 year time horizon was appropriate as it captures the important clinical costs and outcomes without needing to extend beyond the plausible limits of data. The ESC noted that the time horizon used in the model may be too short as patients with CPP are treated early in life and there is no mortality associated with the disease.

6.27 The ESC considered that undertaking a time trade-off study (TTO) to estimate utilities was appropriate as utilities were not available from the trial or from the literature for this condition. The TTO had a 60 year time horizon which was considered reasonable in this context, but the long time horizon may result in lower utilities because of the impact of time preference (which would favour leuprorelin in this case). Both physical and psychological effects of the condition were incorporated into the vignettes for the TTO, but the ESC noted that the wording of some attributes (e.g. "stunted growth") may have introduced bias in the utility study. The ESC noted that the vignettes were retrospective, covering puberty and post-puberty attributes of the condition in each vignette, which was considered reasonable in this context. The utilities derived from the TTO were also considered to be of an order of magnitude that is plausible with when compared with utilities from a population-based study that reported utilities associated with various adult heights (Christensen 2007).

Key drivers of the cost-utility model

Description	Method/Value	Impact
Time horizon	20 years; assumed from 3.5 months trial duration	High, favours leuprorelin
Utility values	[redacted] gain for treated females and [redacted] gain for treated males during puberty and [redacted] gain for treated females and males post-puberty; calculated from time trade-off utility study	High, favours leuprorelin
Age at initiation of therapy	Average age at initiation of 6 years for females and 7 years for males; assumed from expert opinion	High, favours leuprorelin

Source: compiled during the evaluation

Results of the economic evaluation

Step 1: trial-based costs and outcomes			
Step and component	**Leuprorelin 30mg**	**Leuprorelin 11.25mg**	**Increment (95% CI)**
Costs	[redacted]	[redacted]	[redacted]
Percentage of patients achieving a <4mIU/mL suppression of LH at end of month 6	[redacted]	[redacted]	[redacted]
Incremental cost/patient achieving a <4mIU/mL suppression of LH			[redacted]
Step 2: modelled evaluation against no active treatment using cost-utility analysis			
Step and component	**Leuprorelin 30mg**	**No active treatment**	**Increment**
Costs	[redacted]	[redacted]	[redacted]
QALY gained	[redacted]	[redacted]	[redacted]
Incremental cost/QALY gained			[redacted]

Source: Table B.6:1, D.5:1 and D.5:2, p 46 and 89-90 of the submission
Abbreviations: LH = luteinizing hormone, QALY = quality adjusted life year

6.28 The trial based analysis shows that the incremental cost per patient achieving a peak stimulated level of LH of less than 4mIU/mL is [redacted]. The submission appropriately considers that the results from the trial-based evaluation are not particularly relevant to the assessment of cost effectiveness. This is because it is difficult to interpret the value of a patient having peak stimulated LH suppressed to less than 4mIU/mL.

6.29 The ICER of $15,000 - $45,000 per QALY gained from the cost-utility analysis is driven by the utilities generated from the utility study (as no survival benefit is included in the model), by the 20-year duration of the model, and by the age of initiation of therapy. The results of the sensitivity analyses indicate that the model is most sensitive to the age of initiation, with the ICER increasing from $15,000 - $45,000 to $15,000 - $45,000 when the age at initiation falls to 4 years. While the ICER increases for earlier initiation of therapy, younger age at initiation and longer duration of treatment may be associated with increased benefit in terms of final adult height. The ESC noted that height is included in the model but the effect size is uncertain.
For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/year: [redacted]

6.30 The cost of leuprorelin per patient is expected to be [redacted] for a 4-year treatment course, [redacted] per year, or [redacted] per 3-monthly depot injection.

Estimated PBS usage & financial implications

6.31 This submission was not considered by DUSC.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payments ($36.90 per script)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Assuming [redacted] scripts per year as estimated by the submission.

Source: Table E.2:2, p 103 of the submission

6.32 The financial estimates may overestimate the number of prescriptions of leuprorelin required given the assumption of 100% compliance over 4 years treatment as assumed by the submission. Conversely, the financial estimates may be an underestimate as patient numbers may be higher than predicted because of the potential for use in non-progressive or slowly progressive CPP. Advice from the ESA confirmed that approximately 300 children across Australia require treatment, with each requiring an average of 5-6 years of treatment.

6.33 On balance, the figures provide a reasonable estimate of the expected cost to the PBS. There may be additional costs associated with administration and monitoring although these would be less than $10 million per year. Provided use is restricted to patients with progressive CPP, use per year is expected to be less than $10 million in Year 5.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of leuprorelin for the treatment of children with CPP.

7.2 The PBAC agreed that treatment should be initiated by a paediatric endocrinologist, or endocrinologist specialising in paediatrics, and may be continued in consultation with these specialists. The PBAC disagreed with the ESC that the restriction should specify that the patient must have progressive CPP. Initiation criteria should specify that treatment be initiated in patients with CPP onset before the age of 8 years in girls and 9 years in boys.

7.3 The PBAC considered a telephone authority to be appropriate for the initial supply, with an Authority Required (STREAMLINED) listing being appropriate for continuing treatment.

7.4 The PBAC noted the clinical need for PBS listed treatment of CPP and that the sponsor was asked to request PBS listing for leuprorelin for CPP by the Paediatric Medicines Advisory Group. In this regard, the PBAC noted the Consumer Comments that described the benefits of treatment with, and current issues of patient access to, leuprorelin and the strong support for PBS listing from the ESA.

7.5 The PBAC considered that no active treatment was the incorrect comparator as there are very few patients left untreated in clinical practice. It was considered that most patients would receive an off-label GnRH analogue through the hospital system making these the most appropriate comparator. Advice from the ESA indicated that both leuprorelin and goserelin have been widely used across Australia for CPP, with each having approximately 50% of the current market share.

7.6 The PBAC further noted clinical advice from ESA that stated that most patients currently treated with leuprorelin through the hospital system are treated with either 7.5mg monthly or 22.5mg every three months. It was considered appropriate for patients to initiate treatment on lower doses, with dose escalation to 30mg every three months where required. The PBAC noted advice obtained by the TGA delegate confirming that the 30mg three monthly dose is appropriate, however there remains considerable uncertainty regarding the most clinically effective and appropriate dose.

7.7 The PBAC noted that additional data on the treatment of CPP with GnRHas was available but was not presented in the submission. The PBAC noted the Pre-PBAC Response argued that there are no published studies for the use of other GnRHas in CPP and therefore an indirect analysis of these products is not possible as there is no evidence that these off-label products are effective. The PBAC noted the limitations of currently available data. However, it considered that as other GnRHas are currently being prescribed off-label through hospitals around Australia, it would be possible to conduct a clinical and economic comparison of leuprorelin with other analogues.

7.8 The PBAC noted that suppression of the physical signs of puberty is the main aim of treatment as this is a more patient-relevant outcome than suppression of hormone levels. The superior outcomes for lower dose treatment over high dose treatment in the suppression of physical signs of puberty were noted.

7.9 The PBAC is satisfied that leuprorelin provides, for some patients, a significant improvement in suppression of peak stimulated LH levels and suppression of physical signs of puberty over no active treatment.

7.10 The PBAC noted that leuprorelin has an acceptable adverse effects profile, which is similar regardless of dose used.

7.11 The PBAC agreed with the ESC that the time horizon used in the economic model may be too short, but considered the time trade-off study to be appropriate.

7.12 The PBAC noted that current and future patient numbers are uncertain, particularly given current barriers to access the off-label treatment from hospitals for patients in regional and remote areas.

7.13 The PBAC noted a [redacted]

7.14 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 preparation(s).

7.15 The PBAC advised that leuprorelin is not suitable for prescribing by nurse practitioners.

7.16 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LEUPRORELIN (AS ACETATE) modified release [1 syringe] (&) inert substance diluent [1 syringe], 30mg	1	1	Lucrin® Depot Paediatric	VE

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Central Precocious Puberty
PBS Indication:	Central Precocious Puberty
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a paediatric endocrinologist; OR Must be treated by an endocrinologist specialising in paediatrics
Clinical criteria:	-

Population criteria:	Patient must be under 8 years of age (girls) or 9 years of age (boys); OR Patient must have received treatment with a gonadotropin releasing hormone analogue (GnRHa) for this condition prior to 1 April 2015.
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	-
Cautions	-

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LEUPRORELIN (AS ACETATE) modified release [1 syringe] (&) inert substance diluent [1 syringe], 30mg	1	1	Lucrin® Depot Paediatric	VE

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Central Precocious Puberty
PBS Indication:	Central Precocious Puberty
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a medical practitioner in consultation with a paediatric endocrinologist; OR Must be treated by a medical practitioner in consultation with an endocrinologist specialising in paediatrics.
Clinical criteria:	Patient must have previously received PBS-subsidised initial supply of this drug for this condition
Population criteria:	-
Foreword	-
Definitions	-

Prescriber Instructions	-
Administrative Advice	-
Cautions	-

9 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.

10 Sponsor's Comment

AbbVie welcomes the PBAC's decision to list leuprorelin for the treatment of paediatric patients with central precocious puberty on the PBS.