

6.07 TRIPTORELIN, Powder for I.M. injection (prolonged release) 22.5 mg (as embonate) with solvent, syringe and needles, Diphereline[®], Ipsen Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule listing for triptorelin embonate (henceforth referred to as triptorelin) for the treatment of central precocious puberty (CPP).
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus leuprorelin subcutaneous depot injections. Table 1 presents the key components of the clinical issue addressed by the submission.

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

Component	Description
Population	CPP in children 2 years and older with an onset before 8 years in girls and 10 years in boys.
Intervention	22.5 mg triptorelin administered every six months as a single intramuscular injection.
Comparator	Leuprorelin acetate depot 30 mg PDS
Outcomes	<p><u>Primary</u> Percentage of children with luteinising hormone suppression to prepubertal levels 30 minutes after leuprolide stimulation at month 6.</p> <p><u>Secondary</u> Luteinising hormone, follicle stimulating hormone, basal estradiol (in girls) and testosterone (in boys) levels at baseline, on-treatment, end-of treatment, and corresponding changes from baseline. Change in height and growth velocity, sexual maturation, uterine length in girls, and testicular volume in boys. Adverse events.</p>
Clinical claim	For the treatment of central precocious puberty, triptorelin is non-inferior compared to leuprorelin depot 30 mg PDS at suppression with respect to luteinising hormone levels with a comparable safety profile.

Source: Table 1.1.1, p12 of the submission.

CPP = central precocious puberty; mg = milligram; PDS = Prefilled double chamber syringe

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration. The submission was made under TGA/PBS parallel process, with the Delegate's Overview available at time of PBAC consideration. The proposed TGA indication is for the treatment of children 2 years and older with central precocious puberty (CPP). Triptorelin is currently approved for the treatment of hormone-dependent locally advanced or metastatic prostate cancer.

- 2.2 The proposed PBS indication for triptorelin was narrower than the TGA approved indication for leuprorelin that includes no age limit: treatment of children with central precocious puberty (CPP).

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

3 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
Triptorelin Injection, 22.5 mg [1 vial], inert substance diluent [2 mL ampoule]	1	1	0	\$1,839.28	Diphereline® Ipsen Pty Ltd.
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				
Condition:	Central precocious puberty				
Treatment phase:	Initial				
Restriction:	<input checked="" type="checkbox"/> Restricted benefit				
Treatment criteria:	Must be treated by a paediatric endocrinologist; OR Must be treated by an endocrinologist specialising in paediatrics				
Population criteria:	Patient must be aged 11 years or younger (girls) or 12 years or younger (boys), AND Patient must have had an onset of central precious puberty before 8 years (girls) or 10 years (boys).				
Treatment phase:	Continuing				
Restriction:	<input checked="" type="checkbox"/> Restricted benefit				
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 been issued with an authority prescription for a gonadotropin releasing hormone analogue for this condition.				
Treatment phase:	Grandfathered				
Restriction:	<input checked="" type="checkbox"/> Restricted benefit				
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 non-PBS subsidised treatment with this drug for this condition prior to (PBS listing date)				

Source: Table 1.4.1-1.4.4, pp23- 25 of the submission.

- 3.1 The submission did not request a Special Pricing Arrangement. The requested price was the same as the currently listed price of triptorelin for prostate cancer.
- 3.2 The restriction was generally consistent with the TGA indication. However, the draft Product Information (PI) includes a minimum age at which treatment may be initiated of 2 years old, which was not proposed in the restriction.
- 3.3 The continuing criteria proposed by the submission (and reiterated in the pre-PBAC response) specified prior use with a gonadotropin-releasing hormone analogues (GnRHa) treatment, rather than specifically triptorelin. This was inconsistent with the included evidence, which only included treatment naïve patients. The PBAC

considered the proposal in the submission was reasonable as this would allow for clinical decision making autonomy, which would facilitate switching between GnRH analogues for CPP in practice. Triptorelin may be preferred for some patients due to the reduced dosing frequency.

- 3.4 The requested listing of triptorelin allowed treatment initiation for patients up to one year older than the listing of leuprorelin and cessation of treatment with triptorelin at up to 1-2 years older than the current listing of leuprorelin. The Pre-Sub-Committee Response explained that the requested restriction was consistent with the inclusion criteria of the supporting registration studies and the clinical implications of the different age range than the current listing of leuprorelin would be minimal. The ESC considered the clinical decision to cease treatment for CPP (and allow onset of puberty) was a matter of clinical judgment and agreed it was likely the clinical implications of the different age ranges for leuprorelin and triptorelin were minimal. The PBAC agreed with the ESC and considered it was reasonable to align the restriction of triptorelin with the age inclusion criteria of the supporting clinical studies and agreed it was unlikely the differences in ages specified between leuprorelin and triptorelin would substantially alter clinical management of CPP.
- 3.5 The submission requested a ‘grandfather’ restriction to allow transition to PBS-subsidised therapy from a planned product familiarisation program. It was noted that any ‘grandfather’ listing would be expected to capture the same patient population as would the non-‘grandfather’ listings, without requiring the patient to stop treatment such that disease severity deteriorated to meet usual PBS entry criteria. The submission’s proposed ‘grandfather’ restriction, would technically open access to patients commenced on treatment where their age is older than the upper limit in the ‘Initial treatment’ restriction, and/or, CPP symptoms occurred after the specified age ranges in the ‘Initial treatment’ restriction. Therefore, submission’s proposed ‘grandfather’ restriction would need correction.
- 3.6 Triptorelin would be the second GnRH listed on the PBS for CPP. The proposed restriction did not exclude simultaneous use of triptorelin and leuprorelin. The PBAC considered simultaneous use of triptorelin together with leuprorelin was unlikely to occur in practice.

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

4 Population and disease

- 4.1 CPP is generally defined by premature secretion of gonadotropins and subsequent early onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys as well as premature physical signs of sexual development. CPP is a rare disorder with low incidence and prevalence. Globally it has been reported that it occurs in 1 in 5,000 to 10,000 children (Eugster 2019). In 2019 the Drug Utilisation Sub-

Committee (DUSC) estimated that between 2014 to 2018 there were a total of 713 patients with CPP, 102 male patients and 609 female patients (DUSC 2019).

- 4.2 Triptorelin, a gonadotrophin releasing hormone (GnRH) analogue, inhibits gonadotrophin secretion when given continuously and in therapeutic doses. Inhibition of the increased hypophyseal gonadotropic activity in children with central precocious puberty leads to lowering of the LH levels following GnRH (or GnRH analogue) stimulation test and to suppression of oestradiol and testosterone secretion in girls and boys, respectively.

5 Comparator

- 5.1 The submission nominated leuprorelin as the main comparator. This was reasonable.
- 5.2 It was noted during the evaluation that the triptorelin requested restriction (≤ 11 years [girls] or ≤ 12 years [boys]) was slightly broader than the leuprorelin restriction (≤ 10 years [girls] or ≤ 11 years [boys]). Though it is possible that for the targeted population that does not otherwise fall into the leuprorelin restriction, best supportive care could be a relevant comparator, it was unclear if this would occur in clinical practice.

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 that this item received no consumer comments.

Clinical studies/trials

- 6.3 The submission was based on a naïve indirect comparison of one open label non comparative study of triptorelin (Study 301, N=44) with one randomised dose finding trial of leuprorelin (Lee 2012, N=84) and its extension study (Lee 2014, N=72).
- 6.4 Details of Study 301 and Lee (2012/2014) are provided in Table 2.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Triptorelin					
Study 301	44	SAS, OL, 50 week max follow-up	High	CPP	LH suppression/ mean LH
Leuprorelin 3 month 11.5mg depot versus leuprorelin 3 month 30mg depot					
Lee 2012	84	R, OL, 6 month max follow-up	High	CPP	LH suppression/ mean LH
Lee 2014	72	Ext, OL, 36 month max follow-up	High	CPP	LH suppression/ mean LH

Source: pp37-42 of the submission.

DB = double blind; Ext = extension study; CPP = central precocious puberty; LH = luteinising hormone; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised. SAS = single arm study

- 6.5 All three included studies had a high risk of bias. Study 301 (the triptorelin study) was a single-arm, non-randomised, non-comparative study.
- 6.6 Lee (2012) was a randomised open label dose finding trial, comparing 3-month, 11.5 mg depot of leuprorelin to a 3 month, 30mg depot of leuprorelin, and Lee (2014) was its extension study. Lee (2012 and 2014) formed the basis of the leuprorelin listing on the PBS in 2014 (Leuprorelin Public Summary Document (PSD), November 2014). The leuprorelin submission had considered that based on the observation that there were more patients in the 30mg treatment group than the 11.25mg treatment group who achieved suppression of peak stimulated LH levels, leuprorelin 30mg would be significantly better than no active treatment in suppressing LH levels (paragraph 6.9, Leuprorelin PSD, November 2014). As an open label trial that was not placebo controlled, this trial also had a high risk of bias.

Comparative effectiveness

- 6.7 Table 3 presents the submission’s naïve comparison of the Study 301, Lee 2012 and Lee 2014 study arms for mean luteinising hormone (LH) level and proportion of patients maintaining LH suppression at various time points.

Table 3: Comparison of mean LH levels and proportion maintaining LH suppression across studies

		Triptorelin 22.5mg (LH ≤4 IU/L)	Leuprorelin 30 mg - Treatment Naïve (LH <4 IU/L)	Leuprorelin 30 mg - Extension Study (LH <4 IU/L)
Mean luteinising hormone level across time points (95% CI)		2.37 (1.44 - 3.29)	1.73 (1.29 - 2.16)	1.27 (0.92 - 1.62)
Pre-study/baseline	N	44	21	38
	Mean (SD)	27.21 (20.56)	23.5 (16.76)	10.16 (12.66)
Day 1	N	NA	NA	37
	Mean (SD)	NA	NA	1.49 (0.86)
Month 1	N	44	21	NA
	Mean (SD)	2.00 (2.94)	1.9 (1.74)	NA
Month 2	N	44	21	NA
	Mean (SD)	1.96 (4.43)	2.0 (2.25)	NA
Month 3	N	44	20	NA
	Mean (SD)	2.04 (1.45)	1.4 (0.78)	NA
Month 6	N	44	18	36
	Mean (SD)	4.16 (12.26)	1.6 (0.95)	1.62 (0.82)
Month 9	N	44	NA	NA
	Mean (SD)	1.97 (1.42)	NA	NA
Month 12	N	44	NA	32
	Mean (SD)	2.06 (1.61)	NA	1.58 (1.02)
Month 24	N	NA	NA	18
	Mean (SD)	NA	NA	0.88 (0.58)
Month 36	N	NA	NA	11
	Mean (SD)	NA	NA	0.91 (0.49)
Final Visit	N	NA	NA	36
	Mean (SD)	NA	NA	1.15 (0.74)
% maintaining LH suppression 95% CI (over study duration)		90.91 (78.33 - 97.47)	90.5 (77.9 - 100)	99.48 (88.71 - 100.00)
Month 1: % responders (95% CI)		95.45 (84.53 - 99.44)	NA	NA
Month 2: % responders (95% CI)		95.45 (84.53 - 99.44)	NA	NA
Month 3: % responders (95% CI)		93.18 (81.34 - 98.57)	NA	NA
Month 6: % responders (95% CI)		90.91 (78.33 - 97.47)	NA	100 (90.26 - 100.00)
Month 9: % responders (95% CI)		93.18 (81.34 - 98.57)	NA	NA
Month 12: % responders (95% CI)		97.73 (87.98 - 99.94)	NA	96.9 (83.78 - 99.92)
Month 24: % responders (95% CI)		NA	NA	100 (81.47 - 100.00)
Month 36: % responders (95% CI)		NA	NA	100 (71.51 - 100.00)
Final Visit: % responders 95% CI		NA	NA	100 (90.26 - 100.00)

Source: Table 2.6.1 and Table 2.6.2, p82 and p83 of the submission.

Source: Table 2.6.1, p82 of the submission.

NA = not applicable; SD = standard deviation; LH = luteinizing hormone

* Day is month 6 of pivotal lead-in study by Lee et al 2012

6.8 The submission noted a spike in LH levels at Month 6 (4.16) for the triptorelin group. The following explanations were offered:

- One patient performed the Month 6 (day 169) visit on day 183, i.e. 14 days after the scheduled date.
- One patient had a borderline LH value of 5.1 IU/L at Month 6 but at Month 12, his LH was suppressed to a pre-pubertal level (3.2 IU/L).

- One patient with an LH level of 83 IU/L at Month 6, encountered a technical problem with the 1st triptorelin injection. The injection clogged, the needle was changed, and a 2nd injection was required to complete administration. Only one vial of IMP was used. There were no difficulties with the 2nd injection at Month 6, and at Month 12, LH was suppressed to a pre-pubertal level (3.6 IU/L).
- 6.9 Given, the small sample size of the study, the ESC considered it appeared reasonable that the issues described for these three patients would sufficiently account for the spike in LH levels.
- 6.10 Besides these patients, mean LH levels were broadly consistent across the studies. However, mean levels may be more difficult to interpret and less relevant to clinical decision making than proportion of patients with LH suppression.
- 6.11 The submission noted that Study 301 specified suppression to pre-pubertal levels defined as serum LH level ≤ 5 IU/L. The leuprorelin studies however used a different definition of suppression, LH < 4 IU/L. To avoid a potential bias towards the leuprorelin study, a secondary outcome measure from Study 301 which reported the proportion of patients achieving LH levels ≤ 4 IU/L have been used in this comparison. When using the secondary outcome for triptorelin LH levels ≤ 4 IU/L, a small discordance remains as the leuprorelin studies used the narrower threshold of LH < 4 IU/L. This results in the potential for a small bias in favour of triptorelin.
- 6.12 The submission also noted that within Study 301, patients were naïve to treatment. However, in Lee 2012, each strength included treatment naïve and previously treated patients. By definition, in the extension study by Lee 2014, all patients had previously undergone treatment.
- 6.13 The submission considered that patients who have been previously treated with a GnRHa are more likely to be a responder to treatment, therefore, to avoid a potential bias toward leuprorelin in this comparison, patients who were naïve to treatment were used as the basis of comparison.
- 6.14 LH suppression was approximately 90% in both the triptorelin Study 301 arm and the leuprorelin 30mg arm of Lee 2012. Suppression in the leuprorelin extension study (Lee 2014) was at approximately 99%.
- 6.15 Though the analysis had many important limitations, the numerical trends suggested similar LH suppression across the relevant study arms.

Comparative harms

- 6.16 A comparison of AEs by system organ class across the triptorelin and leuprorelin studies is presented in Table 4.

Table 4: Comparison of adverse events by system organ class

	Triptorelin 22.5mg	Leuprolide Acetate 11.25 mg - Treatment Naive	Leuprolide Acetate 11.25 mg - Previous Treatment	Leuprolide Acetate 30 mg - Treatment Naive	Leuprolide Acetate 30 mg - Previous Treatment	Leuprolide Acetate 11.25 mg	Leuprolide Acetate 30 mg
Gastrointestinal disorders	5 11%	0 0%	1 5%	4 19%	1 5%	11 32%	14 37%
General disorders	5 11%	6 29%	6 29%	6 29%	13 62%	16 47%	14 41%
Infections and infestations	21 48%	6 29%	11 52%	5 24%	3 14%	37 100%	18 53%
Nervous system disorders	6 14%	1 5%	4 19%	8 38%	6 29%	5 15%	6 18%

Source: Table 2.6.3, p85 of the submission.

6.17 The numerical trends appear to favour triptorelin. However, given the nature of the comparison and the high risk of bias of the included studies, a claim of non-inferior comparative safety is likely more reasonable.

Clinical claim

6.18 The submission claimed that for children with CPP:

- Triptorelin is non-inferior compared to leuprorelin in terms of efficacy measured as suppression of LH to pre-pubertal levels.
- Triptorelin is non-inferior in safety compared with leuprorelin based on overall and system organ class (SOC) AEs.

6.19 Both claims are based on numerical trends in a naïve comparison of single treatment arms of different studies with high risk of bias. Consequently, the evaluation considered the reliability of these claims is not strong. Nevertheless, the included evidence does not indicate any strong efficacy or safety signals which would point to inferiority of triptorelin. The ESC noted limited evidence was presented for the clinically-relevant outcomes of growth velocity reduction and improved wellbeing; however, despite the limitations of the clinical data presented, the ESC considered the place of GnRH analogues in the treatment of CPP was well-established and the claim of non-inferior comparative efficacy was likely reasonable.

6.20 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable.

Economic analysis

6.21 Table 5 presents key components and assumptions of the submission's cost-minimisation analysis.

Table 5: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Triptorelin is non-inferior compared to leuprorelin in terms of efficacy, measured as suppression of LH to pre-pubertal levels.
Therapeutic claim: safety	Triptorelin is non-inferior in safety compared with leuprorelin based on overall and system organ class (SOC) AEs.
Evidence base	Naïve treatment comparison of Study 301, Lee 2012, Lee 2014.
Equi-effective doses	2 injections of triptorelin (22.5mg) is equi-effective to 4 injections of leuprorelin (30mg).
Direct medicine costs	Triptorelin costs less than leuprorelin in terms of price per year.
Other costs or cost offsets	MBS items used during review appointments.

Source: Table 3.1.1, p93 of the submission.

AE = adverse event; LH = Luteinising hormone; MBS = Medicare Benefits Schedule; SOC = system organ class

6.22 The submission did not explicitly state the equi-effective doses. However, based on the presented cost-minimisation analysis, the implied equi-effective dose was based on dosing over one year:

2 injections of triptorelin (22.5 mg) = 4 injections of leuprorelin (30 mg).

6.23 These equi-effective doses do not account for differences in duration of treatment. Though little evidence is available for length of treatment with each of the treatments in the proposed setting, it is likely that treatment for most patients will be greater than one year. Given the slight differences in the indications and restrictions of triptorelin and leuprorelin, there is a possibility that in practice some patients would be treated for longer with triptorelin. The evaluation considered the extent to which this would be observed in practice is unclear.

6.24 The submission included cost offsets relating to reduced routine and complex appointments from the 6 monthly compared to 3 monthly injection schedule (MBS Items 116 [routine] and 133 [complex]) as well as reduced biochemical testing (MBS Item 66695).

6.25 Although it was reasonable to assume more frequent appointments to administer injections, there was no basis for modelling differences in complex reviews, as these would likely occur at the same rate regardless of frequency of injections.

6.26 Additionally, it is unclear if evaluations may continue to be needed on a more frequent basis than the six-monthly injections of triptorelin, and thus it may be reasonable to assume a smaller number of reduced appointments.

6.27 It was also unclear if biochemical tests would be performed more regularly with more frequent injections. It does not appear that there would be any clinical reason for leuprorelin to require more frequent biochemical tests.

6.28 Overall, the cost-offsets appeared to be overestimated.

6.29 Table 6 presents the results of the submission's cost minimisation analysis.

Table 6: Results of the cost-minimisation analysis

Treatment	AEMP	Injections per year	Annual cost per year
Leuprorelin acetate 30mg for injection, 1 dual chamber syringe -	\$1,071.68	4	\$4,286.72
Triptorelin 22.5 mg for injection, 1 vial	\$1,690.87	2	\$3,381.74
Annual savings without cost offsets			\$904.98
Annual savings with cost offsets			\$1,101.14

Source: Table 3.3.1, p99 of the submission.

AEMP = Approved ex-manufacturer price; DPMQ = dispensed price per maximum quantity; mg = milligram.

6.30 While the claimed offsets may not be realised in practice, the ESC noted that the listing of triptorelin would be cost saving even without the claimed offsets in the cost minimisation analysis as the requested price was based on the triptorelin price for prostate cancer which is less than the cost of leuprorelin for CPP.

Drug cost/patient/year

6.31 Over one year, triptorelin will cost \$3,381.74 (AEMP of \$1,690.87 x 2 injections) compared to \$4,286.72 for leuprorelin (AEMP of \$1,071.68 x 4 injections), as outlined in Table 7 below.

Table 7: Drug cost per patient for proposed and comparator drugs

	Triptorelin Trial	Triptorelin CMA	Triptorelin Financial estimates	Leuprorelin Trial	Leuprorelin CMA	Leuprorelin Financial estimates
Dose	22.5mg every 6 months			30mg every 3 months		
Cost/patient/year	\$3,381.74*	\$3,381.74*	\$3,678.56**	\$4,286.72*	\$4,286.72*	\$4,756.52**

Source: Table 3.3.1, p99 of the submission and "Diphereline Section 4.xlsx"

* Number of injections times the AEMP

** Number of injections times the DPMQ

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC.

6.33 Table 8 presents the data sources and parameter values in the utilisation estimates.

Table 8: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Proportion applicable to indication, based on PBS listings of triptorelin for CPP	100%	Market data	This would not account for a possibly slightly larger market of triptorelin patients due to the wider allowable age range to initiate treatment.
Market share	78.75%	Advisory board	This estimate is difficult to evaluate due to the various factors involved in individual patient preferences for this condition.
Costs			
Appointments	\$83.00	Weighted average of MBS Item 116 and 133	The submission calculated MBS costs consistently with the cost minimisation analysis. Overall, these offsets were likely overestimated.
Biochemical tests	\$30.50	MBS Item 66695	

Source: Tables 4.1.1 and 4.1.2, p102 of the submission.

Drug utilisation sub-committee = DUSC; Medicare Benefits Schedule = MBS; Pharmaceutical Benefits Scheme = PBS

6.34 The slightly broader age in the restriction for triptorelin could potentially broaden the market beyond the current leuprorelin market. It is unclear to what extent this would be observed in practice, but given the rarity of the condition, it is unlikely this would substantially affect financial estimates.

6.35 As with the CMA, cost offsets were likely overestimated.

6.36 Table 9 presents estimated use and financial implications.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of triptorelin						
Cost to PBS less copayments	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Estimated financial implications for leuprorelin						
Cost to PBS/RPBS less copayments	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Net financial implications						
Net cost to PBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Net cost to MBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Net cost to MBS/PBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²

Source: Tables 4.2.3 4.2.4, and Table 4.2.7, p104, Table 4.3.4, p105, Table 4.4.1, p106, Table 4.5.3, p108 and Table 4.5.4, p108 of the submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

6.37 The submission estimated a total net cost saving to the PBS over the first 6 years of listing. Though cost-offsets were likely overestimated, it remained unlikely that listing of triptorelin for CPP would result in a cost to government.

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

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Restricted Benefit listing of triptorelin for the treatment of central precocious puberty (CPP). In making this recommendation, the PBAC considered the evidence presented supported a conclusion that triptorelin is of non-inferior comparative efficacy and safety to leuprorelin for the management of CPP.

7.2 The Committee advised the equi-effective doses were 2 injections of triptorelin (22.5 mg) over one year at 6-monthly intervals = 4 injections of leuprorelin (30 mg) over one year at 3-monthly intervals.

7.3 The PBAC considered the nominated comparator of leuprorelin was appropriate.

7.4 The PBAC noted the clinical evidence for both triptorelin and leuprorelin were open

label studies and only a naïve comparison of these two agents was presented; however considered that the clinical place of gonadotropin releasing hormone (GnRH) analogues in the management of CPP was well established and considered that the evidence presented was adequate given the rarity of the condition and in the context of the established clinical place of these therapies.

- 7.5 Based on the evidence presented, the PBAC considered that triptorelin is likely to be of similar comparative efficacy to leuprorelin for the management of CPP, and considered the justification provided in the submission for three patients who failed to achieve luteinizing hormone (LH) suppression at 6 months outlined in paragraph 6.8 were reasonable.
- 7.6 The PBAC also considered, based on the evidence presented, that triptorelin is of non-inferior comparative safety to leuprorelin for the management of CPP. The Committee noted there was a numerical trend favouring triptorelin in terms of adverse events, however given the risk of bias in both studies and the established risk/benefit profile of GnRH analogues considered a claim of non-inferior comparative safety was reasonable.
- 7.7 The PBAC considered the differences in age ranges between triptorelin and leuprorelin in the registration studies were unlikely to substantially impact clinical practice and it was reasonable for the restrictions for each to reflect the upper subject age ranges in the TGA registration studies. Furthermore, the PBAC also considered it was reasonable to allow flexibility in the restriction for switching between GnRH analogues in continuing therapy as clinically appropriate. The PBAC considered it was reasonable to add a 'grandfather' restriction for 12 months to allow patients to transition from the planned patient familiarisation program. The PBAC considered it was appropriate to remove the grandfather restriction for leuprorelin which has been in place since 2015.
- 7.8 The Committee noted that the submission requested listing of triptorelin at a lower price than the current listing of leuprorelin. The Committee considered the claimed additional offsets for reduced MBS costs due to reduced testing and healthcare professional attendances were poorly justified and likely overestimated.
- 7.9 The PBAC considered the likely uptake of triptorelin was uncertain as the incidence of CPP is low and prevalent patients are likely already treated with leuprorelin but noted that as triptorelin is less costly than leuprorelin, the listing will be cost saving.
- 7.10 The PBAC advised that triptorelin is not suitable for prescribing by nurse practitioners for the management of CPP, consistent with the listing of leuprorelin for the same indication.
- 7.11 The PBAC recommended the following flow-on restriction changes:
 - Add a clause to both leuprorelin and triptorelin CPP listings to the effect of, 'Patient must be undergoing treatment with this drug as the sole PBS-subsidised GnRH for this PBS-indication';

- Remove the existing grandfather restriction from the listing of leuprorelin (11960L) as this now older than 12 months; and
 - Replace the clinical criterion '*Patient must have previously been issued with an authority prescription for this drug for this condition*' with '*Patient must have previously been issued with a PBS prescription for a gonadotropin releasing hormone analogue for this condition*' to allow treatment switching between GnRH analogues; and
 - Clarify that the Treatment Phase is for continuing treatment with this drug or switching GnRH analogue treatment
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because triptorelin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over leuprorelin, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.13 The PBAC noted that this not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add indication as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TRIPTORELIN					
triptorelin 22.5 mg injection [1 vial] (& inert substance diluent [2 mL ampoule], 1 pack	NEW (1)	1	1	0	Diphereline
Restriction Summary / Treatment of Concept: [New 1]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					
Indication: Central precocious puberty					
Treatment Phase: Initial treatment					
Treatment criteria:					
Must be treated by a paediatric endocrinologist; or					
Must be treated by an endocrinologist specialising in paediatrics					
AND					
Population criteria:					
<i>Patient must be of an age that is prior to their 12th birthday if female; or</i>					
<i>Patient must be of an age that is prior to their 13th birthday if male</i>					
AND					
Population criteria:					
<i>Patient must have had onset of signs/symptoms of central precocious puberty prior to their 9th birthday if female; or</i>					
<i>Patient must have had onset of signs/symptoms of central precocious puberty prior to their 10th birthday if male;</i>					
Restriction Summary / Treatment of Concept: [New 2]					
Indication: Central precocious puberty					
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – ‘Grandfather’ arrangements					
Clinical criteria:					
Patient must be receiving treatment with this drug for this condition prior to [1 Month 20XX – insert listing date here]					
AND					
Patient must have met each of: (i) experienced signs/symptoms of central precocious puberty prior to their 9 th birthday, (ii) initiated treatment with this drug prior to their 12 th birthday, if female; or					
Patient must have met each of: (i) experienced signs/symptoms of central precocious puberty prior to their 10 th birthday, (ii) initiated treatment this drug prior to their 13 th birthday, if male					
AND					
Treatment criteria:					
Must be treated by a paediatric endocrinologist; or					
Must be treated by an endocrinologist specialising in paediatrics; or					
Must be treated by a medical practitioner who has consulted one of the above mentioned specialist types, with agreement reached that treatment continue with this drug on this occasion					

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	Administrative advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
Restriction Summary / Treatment of Concept: [New 3]	
	Indication: Central precocious puberty
	Treatment Phase: Continuing treatment with this drug, or, switching gonadotropin releasing hormone analogue therapy
	Treatment criteria:
	Must be treated by at least one of: (i) a paediatric endocrinologist, (ii) an endocrinologist specialising in paediatrics; or
	Must be treated by a medical practitioner who has consulted one of the above-mentioned specialist types, with agreement reached that treatment continue with this drug on this occasion
	AND
	Treatment criteria:
	<i>Patient must be undergoing continuing treatment with a gonadotropin releasing hormone analogue initiated through the PBS for this PBS indication.</i>

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

Flow-on changes:

- 8.2 Delete the leuprorelin 'Grandfather' listing (attached to PBS item code 11960L; Restriction Summary 6425) that is now more than 12 months old.
- 8.3 *Align leuprorelin's continuing treatment restriction to triptorelin's continuing treatment restriction in central precocious puberty, as follows:*

MEDICINAL PRODUCT / medicinal product pack: LEUPRORELIN / leuprorelin acetate 30 mg modified release injection [1 chamber] (& inert substance diluent [1.5 mL chamber], 1 dual chamber syringe
PBS item code/s: 11944P
Restriction Summary / Treatment of Concept: 6422 Restricted benefit (<i>current as at 1 July 2021</i>)
Indication: Central precocious puberty
Treatment Phase: Continuing treatment <i>with this drug, or, switching gonadotropin releasing hormone analogue therapy</i>
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
Must be treated by at least one of: (i) a paediatric endocrinologist, (ii) an endocrinologist specialising in paediatrics; or
Must be treated by a medical practitioner who has consulted one of the above mentioned specialist types, with agreement reached that treatment continue with this drug on this occasion
AND
Clinical criteria:
Patient must have previously been issued with an authority prescription for this drug for this condition
Treatment criteria:
Patient must be undergoing continuing treatment with a gonadotropin releasing hormone analogue initiated through the PBS for this PBS indication.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.