5.12 PREGABALIN,
Tablet 82.5 mg,
Tablet 165 mg,
Tablet 330 mg
Lyrica®CR,
Upjohn Australia Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required (STREAMLINED) listing of a controlled release formulation of pregabalin (pregabalin CR) for the treatment of neuropathic pain in adults under the same restrictions and clinical criteria as the PBS-listed immediate release formulation of pregabalin (pregabalin IR).

1.2 No explicit clinical claim was presented in the submission. The key clinical components are presented in Table 1.

Table 1: Key components of the clinical issue in the submission

Component	Description
Population	Treatment of neuropathic pain in adults
Intervention	Pregabalin CR 82.5 mg, 165 mg and 330 mg controlled release tablets (taken once daily)
Comparator	Pregabalin IR capsules (total daily dose required is administered as smaller doses given twice daily). The submission anticipated that the proposed pregabalin CR strengths will replace a portion of services for existing pregabalin IR strengths in the following manner: Pregabalin CR 82.5 mg strength for pregabalin IR 75 mg strength, pregabalin CR 165 mg strength for pregabalin IR 150 mg strength, and pregabalin CR 330 mg strength for pregabalin IR 300 mg strength.
Outcomes	- (none presented)
Clinical claim	No explicit clinical claim or clinical evidence was presented in the submission. The submission made reference to the TGA clinical evaluation report and approved PI as "supporting information". The TGA clinical evaluation report concluded that with the established bioequivalence based on the total daily exposure between pregabalin CR tablets and pregabalin IR capsules in the Phase 1 studies, and the results of a placebo controlled study of pregabalin CR in adult subjects with PHN, the efficacy with pregabalin CR tablets was considered to have been demonstrated in the proposed indication, neuropathic pain (Clinical Evaluation Report for Lyrica CR, Submission PM-2020-00665-1-1).

Source: compiled during evaluation.
"Extended" release was used interchangeably with "modified" release or "controlled" release in the TGA clinical evaluation report.
CR=controlled release, ER = extended release; IR= immediate release; PHN = postherpetic neuralgia; PI = Product Information; TGA = Therapeutic Goods Administration

2 Background

Registration status

2.1 Pregabalin CR 82.5 mg, 165 mg and 330 mg tablets were registered on the Australian Register of Therapeutic Goods (ARTG) on 10 March 2021 for the treatment of neuropathic pain in adults.

2.2 The table below summarises the international registration status for pregabalin CR.

Table 2: Pregabalin CR international registration status

Country	Submission Date	Approval Status	Approved Indications
United States of America (USA)	15 December 2016	Approved 11 October 2017	Neuropathic pain associated with diabetic peripheral neuropathy (DPN) Postherpetic neuralgia (PHN)
Republic of Korea	15 June 2017	Approved 18 July 2018	Treatment of neuropathic pain in adults

Source: Table 3, p24 of the TGA Clinical Evaluation Report
CR = controlled release.

2.3 A submission from AFT Pharmaceuticals (Au) Pty Ltd, to list an oral solution of pregabalin (20mg/mL, 473 mL) on the PBS for the treatment of neuropathic pain, was considered at the November 2021 PBAC meeting (item 5.25 of the November 2021 agenda). The submission requested an Authority Required (STREAMLINED) listing of pregabalin solution under the same circumstances as the existing listings of pregabalin IR capsules.

3 Requested listing

3.1 The requested listing is presented below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for Max. Qty [a]	Proprietary name and manufacturer
PREGABALIN					
Modified release tablet, 82.5 mg, 30 tablets	1	30	5	$22.94	LYRICA® CR, Upjohn Australia Pty Ltd
Modified release tablet, 165 mg, 30 tablets	1	30	5	$28.75	
Modified release tablet, 330 mg, 30 tablets	1	30	5	$36.95	

[a] The requested DPMQs were revised based on applicable mark-ups and fees as at 1 July 2021.

Category / Program:	GENERAL – General Schedule (Code GE)
PBS Indication:	Neuropathic pain in adults
Treatment phase:	Initial and continuing
Restriction:	☒Streamlined
Clinical criteria:	The condition must be refractory to treatment with other drugs.
Prescriber:	Initial and continuing: Medical Practitioner Continuing: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners
Prescriber instructions:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Source: Table 1.2, p12 of the submission.

3.2 Listing was requested on the PBS "under the same restrictions and clinical criteria" as the currently listed pregabalin IR capsules.

3.3 Pregabalin IR (25 mg, 75 mg, 150 mg and 300 mg capsules, each in a pack size of 56 capsules) are currently PBS listed for the treatment of neuropathic pain.

3.4 No special pricing arrangement (SPA) was proposed in the submission. The requested ex-manufacturer prices for pregabalin CR (82.5 mg, 165 mg and 330 mg tablet strengths) were not cost-minimised to the total daily doses required (refer to paragraph 6.19 further below).

3.5 The Australian Medicines Handbook (Neurological drugs. Adelaide: AMH Pty Ltd, 2020)[1] recommends consideration of uneven dose splitting of IR pregabalin, with the higher dose in the evening as this can improve sleep and reduce daytime sedation. Uneven dose splitting is not possible with pregabalin CR.

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

[1] https://amhonline.amh.net.au/auth?page=chapters/neurological-drugs/antiepileptics/other-antiepileptics/pregabalin (accessed 22 August 2021).

4 Population and disease

4.1 Around 7–8% of adults have pain with "neuropathic characteristics". Approximately 25% and 35% of diabetics and people with HIV infection, respectively, experience neuropathic pain (International Association for the Study of Pain, 2020)[2].

4.2 Examples of neuropathic pain include postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), radiculopathy, and limb amputation. There are several options for drug treatment. Analgesics are usually only partially effective; analgesic adjuvants (such as gabapentin, pregabalin, amitriptyline) are the mainstay of drug therapy and choice of an adjuvant is largely dependent on efficacy, adverse effects/contraindications, need for sedation, and cost. The proposed treatment line for pregabalin CR is similar to that for pregabalin IR, that is, the condition must be refractory to other treatments (refer to Quality Use of Medicines (QUM) further below).

4.3 Pregabalin is marketed in Australia under several brand names including Lyrica® (pregabalin IR). The intervention is pregabalin CR, with three proposed tablet strengths of 82.5 mg, 165 mg, and 330 mg, dosed once daily for neuropathic pain.

4.4 The recommended starting dose is 165 mg once daily, administered after an evening meal. Based on response/tolerability, the dosage may be increased to 330 mg once daily, after an interval of 3 to 7 days. If there is still insufficient pain relief following 2 to 4 weeks of treatment, dose may be increased (if tolerant) by an additional 165 mg/day to 495 mg/day, and then after an additional 7-day interval, by 165 mg/day up to a maximum recommended dose of 660 mg once daily.

4.5 Patients with diabetic neuropathy, in accordance with clinical practice, should be assessed for renal impairment prior to commencing pregabalin CR and dosage adjusted appropriately (Table 3). Pregabalin CR is not recommended for patients with creatinine clearance (CLcr) <30 mL/min or who are undergoing haemodialysis. Those patients should receive pregabalin IR. Dosage adjustment based on renal function is also required for pregabalin IR.

Table 3: Pregabalin CR dosage adjustment based on renal function.

Creatinine Clearance (CLcr) (mL/min)	Pregabalin CR tablets - Daily Dose (mg/day)				Dose Regimen
≥ 60	165	330	495[a]	660[b]	Once a day
30 - 60	82.5	165	247.5[c]	330	Once a day
< 30 / haemodialysis	Dose with pregabalin IR				

Source: Approved PI for pregabalin CR

[a] 495 mg = 3 × 165 mg tablets taken once a day.

[b] 660 mg = 2 × 330 mg tablets taken once a day.

[c] 247.5 mg = 3 × 82.5 mg tablets taken once a day

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

[2] International Association for the Study of Pain, 2020. Neuropathic pain in the community: prevalence, impact, and risk factors.

5 Comparator

5.1 The submission nominated the current PBS-listed pregabalin IR (Lyrica®) capsules as the comparator. There are four available strengths of pregabalin IR capsules on the PBS for the treatment of neuropathic pain: 25 mg, 75 mg, 150 mg, and 300 mg capsules.

5.2 There was no information provided in the submission regarding pregabalin prescribing patterns and the current distribution of pregabalin IR doses for neuropathic pain in Australian clinical practice. This would have been informative to identify which pregabalin IR capsule strengths would be replaced by the various pregabalin CR tablet strengths. Some patients may use equally divided doses whereas others may use a higher dose at night for sedation. The Pre-Sub-Committee Response (PSCR) provided additional analyses using the PBS 10% sample to support revisions to the economic analysis and financial estimates (discussed further in the sections below). The ESC considered data provided was reasonable to inform how substitution of pregabalin IR to CR may occur in practice.

5.3 A comparison of pregabalin CR and pregabalin IR is summarised in the table below.

Table 4: Comparison of pregabalin IR and pregabalin CR

Comparison	**Comparator** **Pregabalin IR**	**Proposed medicine** **Pregabalin CR**
Drug class	Gabapentinoid	
Approved TGA indications	Neuropathic pain in adults Adjunctive therapy in adults with partial seizures with or without secondary generalisation.	Neuropathic pain in adults Efficacy of pregabalin CR has not been established in fibromyalgia or as an adjunctive therapy for adult patients with partial seizures with or without secondary generalisation.
Course of treatment	Capsules, administered orally, in two divided doses (with or without food). Starting dose: 150 mg per day, given as two divided doses. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day, given as two divided doses, after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval. Effectiveness in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than 12 weeks. The risks and benefits of treatment should be assessed before extending therapy for longer than 12 weeks	Tablets, administered orally once daily after an evening meal. Starting dose: 165 mg once daily. Based on individual patient response and tolerability, the dosage may be increased to 330 mg once daily, after an interval of 3 to 7 days. In patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 330 mg once daily and who are able to tolerate, dose may be increased by an additional 165 mg/day to 495 mg/day and then after an additional 7-day interval by 165 mg/day up to 660 mg once daily. The maximum recommended dose is 660 mg once daily. Effectiveness in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than 19 weeks. The risks and benefits of treatment should be assessed before extending therapy for longer than 19 weeks
Conversion from pregabalin IR capsules to pregabalin CR Tablets as indicated in the approved PI for pregabalin CR.	**Pregabalin IR Capsules** **Total Daily Dose** **(dosed twice daily)**	**Pregabalin CR Tablets** **Total Daily Dose** **(dosed once daily)**
	75 mg / day	82.5 mg / day
	150 mg / day	165 mg / day
	225 mg / day	247.5 mg / day[a]
	300 mg / day	330 mg / day
	450 mg / day	495 mg / day[b]
	600 mg / daily	660 mg / day[c]
	Note: When switching from pregabalin IR to pregabalin CR on the day of the switch, patients should take their morning dose of pregabalin IR as prescribed and initiate pregabalin CR therapy after an evening meal. [a] 247.5 mg = 3 × 82.5 mg tablets taken once a day [b] 495 mg = 3 × 165 mg tablets taken once a day. [c] 660 mg = 2 × 330 mg tablets taken once a day.	

Comparison	Comparator Pregabalin IR	Proposed medicine Pregabalin CR
	IR = immediate release; CR = controlled release	
Proposed/approved PBS restrictions	Listed Neuropathic pain The condition must be refractory to treatment with other drugs.	Proposed Neuropathic pain The condition must be refractory to treatment with other drugs. Pregabalin CR is not proposed for fibromyalgia or acute pain or chronic pain of non-neuropathic origin.
Toxicities/contraindications/special populations (or other characteristics) that may result in differences in use	Indicated for CLcr less than 30 mL/min with dosage adjustment required	Not recommended for patients with CLcr less than 30 mL/min or who are undergoing haemodialysis. Those patients should receive pregabalin IR.
Any differences that may result in changes in patient compliance	-	The submission stated that pregabalin CR once daily dosing is expected to enhance compliance/adherence compared to the IR formulation, which is administered in two or three divided doses. The approved Product Information recommends that the total daily dose of pregabalin IR should be administered in two divided doses. No evidence was presented in the submission to demonstrate adherence is improved with the CR formulation compared with the IR formulation.

Source: Compiled during the evaluation from Section 1 of the submission, the approved Product Information for pregabalin IR and pregabalin CR, and PBS online.

[a] TGA Clinical Evaluation Report for pregabalin CR (Submission PM-2020-00665-1-1, Section 4.3, p 36).

IR = immediate release; CR = controlled release; CLcr = creatinine clearance; TGA = Therapeutic Goods Administration; PI = Product Information

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 the advice received from Musculoskeletal Australia outlining three patient experiences of being treated with immediate release pregabalin. All three patients offered minimal support for listing of pregabalin CR due to the negative side effects and limited benefits of pregabalin treatment for pain.

Clinical studies

6.3 No comparative clinical evidence or explicit clinical claim was presented in the submission. The submission noted that the key/supporting evidence was based on an adequate and well-controlled 19-week randomised placebo controlled trial of daily

doses of pregabalin CR 82.5 mg, 165 mg, 247.5 mg, 330 mg, 495 mg, or 660 mg strengths in adults with PHN. The submission referred to supporting information in the TGA clinical evaluation report and the PI for pregabalin CR.

6.4 Of note, "modified" release or "extended" release (ER), or "controlled" release (CR) were used interchangeably in the clinical evaluation report for pregabalin CR.

Comparative effectiveness

6.5 In the absence of a clinical comparison being presented in the submission, relevant advice from the TGA Delegate from the CER is presented below.

6.6 Pregabalin CR tablets demonstrated linear pharmacokinetics (PKs) with dose-proportional increases in maximum observed concentration (Cmax) and area under the curve (AUC) with once daily doses ranging from 82.5–660 mg.

6.7 Pregabalin CR tablets administered once daily (82.5 mg to 660 mg), following an evening meal, have equivalent AUC and lower Cmax relative to a comparative dose of pregabalin IR capsules administered without food twice daily or three times daily (75 mg/day to 600 mg/day).

6.8 Across the studies, the relative bioavailability of the pregabalin CR tablets was approximately 93% to 97% of pregabalin IR capsules when given once daily after a 600-750 calorie medium-fat evening meal.

6.9 The pregabalin CR doses utilised in the pregabalin CR randomised placebo-controlled study (Study 1224) were designed to correspond to pregabalin IR doses used in the treatment of neuropathic pain, based upon the results of the Phase 1 studies, with adjustment of treatment doses for CLcr, and flexible dosing during the single blinded (SB) phase to allow tailored dose optimization.

6.10 In Study 1224, the time to loss of therapeutic response (LTR) was statistically significantly longer with pregabalin CR compared to placebo, with fewer pregabalin CR treated subjects (13.9%) experiencing LTR during the double blinded (DB) phase compared to placebo treated subjects (30.7%).

6.11 The evaluator agreed that with the established bioequivalence, based on the total daily exposure between pregabalin CR tablets and pregabalin IR capsules in the Phase 1 studies, and the results of Study 1224 in adult subjects with PHN, the efficacy of pregabalin CR tablets was considered to have been demonstrated in the proposed indication, neuropathic pain. The change in formulation/pharmacokinetic profile did not affect the efficacy relative to that observed for the pregabalin IR formulation.

6.12 Worthy of note is that the efficacy of pregabalin CR, versus placebo, in the treatment of neuropathic pain has not been assessed for treatment periods of longer than 19 weeks. The risks and benefits of treatment should be assessed before extending therapy for longer than 19 weeks. This differs for pregabalin IR (Section 4.2 of the approved PI) which has not been assessed for treatment periods longer than 12

weeks. The risks and benefits of pregabalin IR for neuropathic pain should be assessed before extending therapy for longer than 12 weeks.

Comparative harms

6.13 In the submitted studies, pregabalin CR tablets with doses ranging from 82.5 mg to 660 mg administered once daily after an evening meal were shown to be generally safe and well tolerated, with no evidence of a dose-dependent pattern of events.

6.14 Reported cases of events of interest (dizziness, somnolence, oedema, weight gain, gastrointestinal disorders, and euphoric mood) in the submitted Phase 3 studies of pregabalin CR were consistent with the known effects of pregabalin IR. There were no clinically significant differences between pregabalin CR and placebo in terms of laboratory tests, vital signs and physical examination findings.

6.15 The overall safety profile of pregabalin CR tablets appeared to be consistent with that seen with pregabalin IR capsules. Most adverse events (AEs) were mild to moderate in severity.

6.16 The submission did not provide information on potential safety concerns. Post-marketing experience in the US indicated that prescribing errors occurred in 11.2% of cases, which mostly involved prescribing IR doses instead of extended release doses (such as 75 mg instead of 82.5 mg or 300 mg instead of 330 mg). Given that these formulations are dosed differently (pregabalin IR twice daily and pregabalin CR once daily), there are safety and pain control implications for patients should these prescribing errors occur. The PSCR stated that risk of prescribing error was not raised during TGA evaluation.

Clinical claim

6.17 No explicit clinical claim was presented in the submission. However, the submission stated that a cost minimisation approach was taken to establish the pricing of pregabalin CR tablets relative to the currently listed pregabalin IR capsules. This is consistent with a claim of non-inferiority.

6.18 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonably supported by the data.

Economic analysis

6.19 No formal economic analysis was presented in the submission; rather, the PI daily dose relativity (1.1 : 1 pregabalin CR : pregabalin IR) was implicitly assumed to represent equi-effective doses, and the proposed pricing of pregabalin CR 82.5 mg tablets, 165 mg tablets and 330 mg tablets was directly based on the price of pregabalin IR 75 mg capsules, 150 mg capsules and 300 mg capsules, respectively (converting current 28-day supply to proposed 30-day supply).

6.20 The submission matched the daily price of the CR formulation to the 1.1: 1 equivalent IR capsule strength, not the IR total daily dose (TDD). Given the IR is dosed twice daily,

the original approach effectively applied a TDD relativity of 0.55:1, which does not represent equi-effective substitution. The PSCR acknowledged the incorrect matching of the daily price of CR formulation to the IR strength and agreed that CR formulation should match the IR TDD. The sponsor proposed lower AEMP as shown in the table below.

Table 5: PSCR revised pricing proposal for pregabalin CR packs

Medicine	Tablets per pack	AEMP [a]	Total tablets per script
Pregabalin 82.5mg modified release tablet	30	$5.60	30
Pregabalin 165mg modified release tablet	30	$8.00	30
Pregabalin 330mg modified release tablet	30	$10.11	30

Abbreviations: AEMP = approved ex-manufacturer price

[a] Prices take into consideration the price reduction for pregabalin announced for October 2021 as a result of price disclosure.

6.21 Revised comparison of the proposed prices and TDD costs undertaken in the PSCR, based on the dose regimen distributions derived from the PBS 10% sample is presented in the table below. The PSCR noted that both 225 mg TDD and 450 mg TDD are not cost-minimised when converted to CR formulations, and argued that the PBS 10% sample data indicated the proportional use of the 225 mg and 450 mg daily regimens of pregabalin would likely have a minimal financial impact, even though the proposed prices would make the equivalent CR prices marginally more expensive.

Table 6: Results of the cost-minimisation based on total daily dose (TDD) – recalculated with the new IR prices (post October 2021) and new proposed CR prices – reworked

Pregabalin IR		Pregabalin CR		Additional daily cost associated with CR	% of total population on this dose [c]	as a % of total eligible population (70.8%)
Total Daily Dose (dosed twice daily)	Cost per TDD [a] (A)	TDD (dosed once daily)	Cost per TDD [b] (B)	(B – A)		
75 mg / daily	$0.20	82.5 mg / daily	$0.19	-$0.01	35.3%	49.9%
150 mg / daily	$0.29	165 mg / daily	$0.27	-$0.03	22.0%	31.1%
225 mg / daily	$0.37	247.5 mg / daily [d]	$0.45	$0.08	2.7%	3.9%
300 mg / daily	$0.45	330 mg / daily	$0.34	-$0.12	9.8%	13.9%
450 mg / daily	$0.56	495 mg / daily [d]	$0.60	$0.04	0.9%	1.3%
600 mg / daily	$0.67	660 mg / daily	$0.67	-$0.00	[e]	
					70.8%	100.0%

[a] Total daily dose cost for IR were calculated using the confirmed October 2021 AEMP published on https://www.pbs.gov.au/info/industry/pricing/price-disclosure-spd; pharmacy and wholesaler mark-ups were not considered as they do not relate to the cost of the medicine.

[b] Total daily dose cost for equivalent CR dose were calculated using the proposed pricing shown on table 3.2 above.

[c] Source: Medicare 10% data as at end Dec 2020.

[d] Alternative combination that achieves the same TDD were not considered as those combinations are unlikely to be prescribed given little or no clinical or economic benefit to the patient (i.e., using 1 dose of 165mg plus one dose of 82.5mg achieves the same TDD of 247.5mg with less pills and less cost than using 3 doses of 82.5mg) This is reasonable based on lower cost compared to the cost of using 3 x 82.5 mg and 3 x 165 mg tablets taken once a day, which is prescribed for conversion from pregabalin IR to pregabalin CR in the approved PI.

[e] Source of data only specifies that 450mg+ dose usage is 0.9% of the total without indicating the usage percent for 600mg. Both the 450mg and the 600mg usage proportion are below 0.9% both individually and in the combined.

6.22 The ESC considered, on balance, the revised cost-minimisation based on the TDD approach presented in the PSCR appeared to be reasonable.

6.23 Pregabalin IR is in Formulary 2 and will be subjected to price disclosure during the cycles in October 2021 and April 2022. It is unlikely that cost-minimisation based on current prices will remain the same, however the magnitude of price reductions cannot be determined prospectively.

Drug cost/patient/year

6.24 The cost/patient/year given below is based on the requested DPMQs (which are revised during evaluation based on applicable mark-ups and fees as at 1 July 2021). The DPMQs of pregabalin CR 82.5 mg, 165 mg and 330 mg are $22.94, $28.75 and $36.95 respectively. There are 30 tablets per pack which is sufficient for a 30 day supply (12.18 scripts per year, as calculated by the submission. However, to achieve some of the approved dose regimens, patients will require multiple packs to achieve doses equivalent to IR pregabalin, e.g. a 165 mg pack and an 82.5 mg pack are required for a daily dose of 247.5mg.

6.25 Due to the approach used in the economic evaluation and financial estimates, it was difficult to reliably determine the drug cost/patient/year listed in table below. This is highly uncertain given the concerns in the requested price for pregabalin CR, which is not cost-minimised (paragraph 6.19) based on total daily doses. The PSCR provided an amended drug cost/patient/year table based on the revised pricing proposal and CMA based on a TDD approach. The sponsor noted that 225 mg TDD, 450 mg TDD and 600 mg TDD (5.1% of the total eligible pool) are not cost-minimised if converted to CR. However, the sponsor argued these doses are unlikely to be converted to CR pregabalin in practice and noted the overall revised price proposals result in an overall lower price across the distribution of dose regimens based on the PBS 10% sample data.

Table 7: Script and drug cost / patient / year equivalence between pregabalin IR and proposed Lyrica CR

Pregabalin IR			Pregabalin CR			Additional yearly total drug cost associated with CR (B – A)	% of total population on this dose [c]	as a % of total eligible population (70.8%)
Total Daily Dose (dosed twice daily)	scripts / patient / year	Drug cost / patient / year [a] (A)	TDD (dosed once daily)	scripts / patient / year	Drug cost / patient / year [b] (B)			
75 mg / daily	19.57	$317.38	82.5 mg / daily	12.18	220.38	-$97.00	35.3%	49.9%
150 mg / daily	13.04	$273.29	165 mg / daily	12.18	251.80	-$21.49	22.0%	31.1%
225 mg / daily	13.04	$304.22	247.5 mg / daily [d]	24.35	472.18	$167.96	2.7%	3.9%
300 mg / daily	13.04	$335.14	330 mg / daily	12.18	279.42	-$55.72	9.8%	13.9%
450 mg / daily	13.04	$378.76	495 mg / daily [d]	24.35	531.22	$152.46	0.9%	1.3%
600 mg / daily	13.04	$422.38	660 mg / daily	24.35	558.84	$136.46	[e]	
							70.8%	100.0%

[a] Calculated using DPMQ for pregabalin IR from October 2021 (inclusive of price disclosure price drop) based on DPMQs for 25mg=$16.22, for 75mg=$20.95, for 150mg=$25.69, and for 300mg=$32.38), as calculated by the PSCR.

[b] Calculated using DPMQ derived from proposed Lyrica CR AEMP (DPMQ for 85.2mg=18.10, for 165mg=20.68, and for 330mg=22.95)

[c] Source: Medicare 10% data as at end Dec 2020.

[d] Alternative combination that achieves the same TDD were not considered as those combinations are unlikely to be prescribed given little or no clinical or economic benefit to the patient (i.e. using 1 dose of 165mg plus one dose of 82.5mg achieves the same TDD of 247.5mg with less pills and less cost than using 3 doses of 82.5mg) This is reasonable based on lower cost compared to the cost of using 3 x 82.5 mg and 3 x 165 mg tablets taken once a day, which is prescribed for conversion from pregabalin IR to pregabalin CR in the approved PI.

[e] Source of data only specifies that 450mg+ dose usage is 0.9% of the total without indicating the usage percent for 600mg. Both the 450mg and the 600mg usage proportion are below 0.9% both individually and in the combined.

Estimated PBS usage & financial implications

6.26 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC). The submission used a market-share approach to predict the likely use and financial impact of listing of pregabalin CR on the PBS. This approach was reasonable given the maturity and stability of the pregabalin IR, which was PBS listed on 1 March 2013.

6.27 The submission used a market-share approach to estimate the utilisation of pregabalin CR tablets. The submission noted that the proposed pregabalin CR 82.5 mg, 165 mg and 330 mg will replace a portion of services for pregabalin IR 75 mg, 150 mg and 330 mg respectively.

6.28 The key inputs for the financial estimates are summarised below.

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

Data	Value	Source/Comment
Market Size	PBS Statistics (2013 – 2020) for PBS items 2348N, 2335X, 2355Y and 2363J (pregabalin IR 25 mg, 75 mg, 150 mg and 330 mg capsules, respectively).	This data source was appropriate. The submission stated that the market is mature and stable (pregabalin was PBS listed on 1 March 2013). The historic PBS data shows a negative growth for 2019-2020.
Market growth for current listing	Annual growth of 2% through Year 1 to Year 6	Assumption. The sponsor did not provide any rationale for this assumption. This assumption is uncertain and not justified given the recent declining trend in market growth. The submission stated that the proposed listing of pregabalin CR was not expected to increase the overall market utilisation. During the evaluation the cells in the spreadsheet were changed according to assumptions stated in the main text of the submission (input changed from 0% to 2% in: 2d. Scripts – market, cells D105, D117, D129, and D141). The PSCR noted that the assumed market growth of 2% was based on a number of factors, including the total overall pregabalin IR market, changing trends to a higher proportion of private market prescribing and demographic growth and argued this assumption was conservative overall.
Script equivalence	1 script pregabalin IR = 0.93 script pregabalin CR	Calculation. 1 script of pregabalin IR (56 capsules, 2 capsules per day) can be replaced by 0.93 script of pregabalin CR (30 tablets, 1 tablet per day). This is highly uncertain because it is only applicable to the one for one low-dose/high-dose (excluding 25 mg capsules) substitution proposed by the submission. However, there are various substitution scenarios to achieve required total daily doses prescribed in the pregabalin IR PI, which result in a range of script equivalences of 0.62-1.87.
Treatment utilisation		
Number treated	Ranging from 100,000 to < 200,000 in Year 1 to 800,000 to < 900,000 in Year 6.	Calculated based on the 2% market growth assumption.
Proportion of Pregabalin IR scripts replaced by Pregabalin CR	Year 1: 5.78% Year 2: 17.22% Year 3: 24.09% Year 4: 28.38% Year 5: 32.45% Year 6: 32.45%	Calculation/assumption. The 10% PBS sample was used to determine initial versus continuing script proportions, to then apply differential uptake rates. Assuming the same uptake rate across all capsule strengths, with no information on dose distribution of pregabalin IR, may not be appropriate. Additionally, the forecasted pregabalin IR market used in this calculation is much higher than the estimated script numbers in Section 4.2.
Scripts dispensed for Pregabalin CR	From: 100,000 to < 200,000 in Year 1 to 800,000 to < 900,000 in Year 6.	Assumption. This is highly uncertain. There is limited information to inform how replacement or substitution of pregabalin IR will occur and the distribution of doses likely to be used for neuropathic pain

Source: Table compiled during evaluation from Section 4 of the submission and Excel workbook "LYRICA CR - v.2.Jul.2021 - (UCM-v.106)"
CR = modified release, DPMQ = dispensed price for maximum quantity, IR = immediate release, PBS = Pharmaceutical Benefits Schedule, RPBS = Repatriation Schedule of Pharmaceutical Benefits

6.29 The estimated use and financial implications of listing pregabalin CR on the PBS are summarised below.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total script numbers – Pregabalin CR[a]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of pregabalin CR						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated financial implications for pregabalin IR						
Cost to PBS/RPBS less copayments	-[redacted][4]	-[redacted][4]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	-[redacted][4]	-[redacted][4]	-[redacted][4]	-[redacted][4]	-[redacted][5]	-[redacted][5]

Source: Table compiled during evaluation and revised during the ESC advice process based on the PSCR from Excel workbook "LYRICA CR - v.21 Sep 2021.2021 - (UCM-v.106)"

[a] Assuming 12.08 scripts per year dispensed as estimated by the submission.

The redacted values correspond to the following ranges:

[1] 30,000 to < 40,000

[2] 100,000 to < 200,000

[3] 200,000 to < 300,000

[4] $0 to < $10 million

[5] $10 million to < $20 million

6.30 The revised financial estimates in the PSCR estimated that there would be total savings to the PBS/RPBS from the listing of pregabalin CR, which was estimated to be net cost saving in Year 6, and a total of approximately net cost saving in the first 6 years of listing.

6.31 The revised estimates in the PSCR based on the reduced prices calculated in the revised CMA and revised dose regimen distributions estimated a net save to the PBS, substantially higher than proposed in the initial submission. Whether the proposed savings will be realised in practice remains uncertain. However, given the further-reduced proposed price in the PSCR, the ESC considered it was unlikely the listing of pregabalin CR would result in a cost to government.

6.32 The submission stated that the proposed listing of pregabalin CR 82.5 mg, 165 mg and 330 mg tablets were likely to replace a proportion of the currently listed pregabalin IR 75 mg, 150 mg and 300 mg capsules, respectively. The submission did not expect that the proposed listing will replace any use of pregabalin IR 25 mg capsule. This one for one substitution assumption is highly uncertain. Pregabalin CR 82.5 mg tablets can replace pregabalin IR 25 mg and 150 mg capsules, rather than pregabalin 75 mg capsules as suggested by the submission (it is unlikely that the once daily 75 mg IR capsules will be replaced by once daily dosing of 82.5 mg CR tablets). Pregabalin CR 165 mg tablets can replace pregabalin IR 75 mg and 300 mg capsules in addition to the pregabalin IR 150 mg capsules and pregabalin CR 330 mg tablets can replace pregabalin IR 150 mg capsules in addition to the pregabalin 300 mg capsules as anticipated by the submission. Given the lack of information about clinical dosing patterns and substitutions, the Commentary could not re-estimate the expected financial impact. Revised estimates based on the PBS 10% Sample were provided in

the PSCR, however uncertainty as to how pregabalin IR may be replaced by the CR formulation in practice remains.

Quality Use of Medicines

6.33 Post marketing data for pregabalin CR in the United States (US) indicated there is the potential for prescribing errors regarding pregabalin CR and pregabalin IR. These formulations are dosed differently (once daily and twice daily, respectively) and there may be implications for safety or for suboptimal control of neuropathic pain. The Pre-PBAC Response noted prescribing error risk was not raised as a concern by the TGA during formulation of the Risk Management Plan (RMP) for pregabalin CR and stated an informal review of the safety database for pregabalin showed few spontaneous adverse drug reaction reports for pregabalin CR and did not suggest a pattern of prescribing errors.

6.34 Australian ambulance data in 2018 showed a tenfold increase in the rate of pregabalin-related ambulance attendances since 2012, with patients frequently misusing pregabalin with other sedating medicines[3].

6.35 In 19 January 2021, the TGA's Database of Adverse Event Notifications included 184 and 18 reports of suspected abuse/misuse/dependence with pregabalin and gabapentin products, respectively. There were 111 fatal cases and for 110 of these, pregabalin was the suspected medicine. The Advisory Committee on Medicines (ACM) noted the following (ACM Meeting Statement, Meeting 13, 1 February 2019, Gabapentinoids and risk of harmful and hazardous use):

> Premarket studies for pregabalin suggested a low potential for abuse, however such studies commonly excluded people with a history of substance abuse. People with depression, people who concomitantly use opioids and/or benzodiazepines, and young men are at higher risk of harmful and hazardous use of pregabalin.

6.36 Pregabalin appeared to have a higher addictive potential than gabapentin. The committee considered there to be sufficient and compelling evidence of a strong signal for the harmful and hazardous use of pregabalin. The committee noted that the evidence included multiple sources from Australia and internationally, including data regarding fatalities, drug utilisation, prescribing patterns, adverse event reporting, and trends in intentional poisonings. The committee accepted the conclusion of Cairns et al (2018)[4] that 'One in seven Australians dispensed pregabalin appears to be at high risk of misuse'.

6.37 The QUM issues identified for pregabalin IR in the 24 month DUSC report (pp37-9, Public Release Document, October 2015 DUSC Meeting) are also likely to be relevant

[3] Pregabalin and gabapentin Safety Advisory on TGA https://www.tga.gov.au/alert/pregabalin-and-gabapentin: accessed 19 August 2021

[4] Cairns R, Schaffer AL, Ryan N, et al. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. Addiction 2018. doi:10.1111/add.14412.

to pregabalin CR. These include use for other conditions without being on a prior drug regimen (approximately 45%), lack of significant reduction of strong opioid use or other neuropathic pain medicines, pregabalin may not be reaching patients with the most need for currently available alternative treatments pain and the uncertainty of discontinuation due to adverse effects or adequate benefit from the dose prescribed.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of a controlled-released formulation of pregabalin (pregabalin CR) for the treatment of neuropathic pain to allow for utilisation analysis of immediate release pregabalin (pregabalin IR) and to further consider the potential quality use of medicines (QUM) issues with the CR formulation.

7.2 The PBAC was concerned about reports of potential misuse and diversion of pregabalin (and gabapentinoids more broadly) in Australia. The Committee therefore considered it was prudent to review the utilisation of pregabalin and to consider current evidence of misuse and diversion of pregabalin in Australia prior to forming a view as to whether other forms of pregabalin should be recommended for listing on the PBS. The PBAC referred the matter of pregabalin use to the DUSC for consideration at a future meeting.

7.3 The PBAC considered the nominated comparator of pregabalin IR was appropriate.

7.4 With regards to potential QUM issues with the CR formulation, the PBAC noted the post-marketing data in the USA indicated substantial levels of prescribing errors and also noted the sponsor argued this had not been raised as an issue during the TGA evaluation and that an 'informal' review of pregabalin adverse events did not suggest an issue. Overall, the PBAC considered, given the international experience, that such errors could also occur in Australia. Furthermore, the PBAC considered the difference in dosing regimen between pregabalin IR (dosed twice daily) and pregabalin CR (dosed once daily) may cause confusion among patients and clinicians, especially for those switching between forms. On that basis, the PBAC considered it may be reasonable to consider additional restriction wording to discourage two-way switches between the IR and CR forms of pregabalin. The PBAC also noted patients with moderate renal impairment would likely require dose adjustment with pregabalin CR compared to the IR formulation and considered this had the potential to create further confusion for prescribers and patients.

7.5 While the submission did not make an explicit clinical claim, the PBAC agreed that a claim of non-inferior comparative safety and efficacy to pregabalin IR was likely reasonable. However, in accepting such a claim, the PBAC reiterated its views there are likely QUM issues associated with the introduction of pregabalin CR. The PBAC also noted that although the only clinical evidence for pregabalin CR was in post-herpetic neuralgia (PHN), the TGA had been satisfied to register pregabalin CR for a broader

neuropathic pain indication.

7.6 The PBAC noted the cost-minimisation analyses presented in the submission incorrectly matched the daily price of pregabalin CR formulation to the 1.1:1 equivalent pregabalin IR capsule, however agreed with the ESC and considered the revised cost-minimisation based on the total daily dose (TDD) approach presented in the PSCR, which used PBS 10% sample data to inform the dose forms used in practice, appeared to be reasonable.

7.7 The PBAC agreed with the evaluation and considered the assumed uptake of pregabalin CR was poorly justified but acknowledged there was limited available data upon which to reliably estimate its use in practice. At the revised price proposed in the PSCR, the PBAC considered it was unlikely the listing of pregabalin CR would result in a cost to the PBS.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.