

**5.19 RELUGOLIX WITH ESTRADIOL AND WITH
NORETHISTERONE ACETATE,
Tablet containing relugolix 40 mg with estradiol (as
hemihydrate) 1 mg and with norethisterone acetate
0.5 mg,
Ryeqo[®],
Gedeon Richter Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested reconsideration of the utilisation and financial estimates of the General Schedule Authority Required (STREAMLINED) listing for the treatment of moderate to severe pain associated with endometriosis.
- 1.2 At its March 2024 meeting, the PBAC recommended listing of relugolix with estradiol and with norethisterone acetate (Ryeqo) for the treatment of moderate to severe pain associated with endometriosis in women who have failed to gain adequate pain relief from hormonal treatments and analgesics.
- 1.3 The submission stated that the risk sharing arrangement (RSA) recommended by the PBAC, with a 1% rebate for use over the subsidisation caps based on the estimates outlined in the Ratified Minutes (March 2024 Public Summary Document [PSD], Table 13), was significantly underestimated and poses an unreasonable financial risk. The submission presented re-estimates informed by a new clinician survey, and requested that the PBAC reconsider the annual expenditure caps and the percent rebate for all use beyond the caps.

2 Background

Registration status

- 2.1 Ryeqo was TGA registered for this indication on 31 January 2024. The indication in the approved Product Information (PI) was:

‘Ryeqo is indicated in adult women of reproductive age for:
Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis’
- 2.2 The approved PI also includes the following advice regarding bone mineral density (BMD) loss:

‘Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and after one year of treatment.

Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.

Annual DXA is recommended while taking Ryeqo'

Previous PBAC consideration

- 2.3 At its March 2024 meeting, PBAC recommended the listing of Ryeqo, on the basis that it should be available as a General Schedule Authority Required (STREAMLINED) listing for the treatment of moderate to severe pain associated with endometriosis in women who have failed to gain adequate pain relief from hormonal treatments and analgesics. The PBAC’s recommendation for listing was based on its assessment that the cost-effectiveness of Ryeqo would be acceptable if it were no more costly over a 12-month period than 12 months of gonadotropin-releasing hormone (GnRH) therapy (plus add-back therapy) as currently supplied through the PBS. The PBAC noted based on current PBS restrictions that GnRH therapy is available as 6 months of goserelin and 6 months of nafarelin. The PBAC acknowledged that Ryeqo would be used on average for more than 12 months and considered the cost calculated for the first 12 months of therapy provides an appropriate frame of reference for the cost of therapy beyond 12 months. The PBAC noted that based on the proposed price, the cost of Ryeqo®, including BMD monitoring and goserelin implantation costs, was lower over 12 months than the comparator costs and was therefore considered cost-effective (paragraph 7.1, relugolix with estradiol and with norethisterone acetate, PSD, March 2024 PBAC meeting).
- 2.4 The PBAC considered that the listing of Ryeqo, as a fixed dose combination (FDC), with the potential for ongoing treatment for 2 years or longer, is likely to result in a substantial net cost to the PBS as it would be used for longer than the existing therapies. The PBAC considered that the financial estimates had a high level of uncertainty due to uncertain prevalence and uptake estimates but considered that the revised estimates presented in the pre-PBAC response were substantially overestimated. The PBAC advised that additional revisions to prevalence and uptake were required as well as a risk sharing arrangement (RSA) with % caps to manage the uncertainties in the financial estimates (paragraph 7.2, relugolix with estradiol and with norethisterone acetate PSD, March 2024 PBAC meeting).

Table 1: Summary of key matters of concern

Component	Matter of concern	How this submission addresses it
Number of treated patients and utilisation of Ryeqo	The PBAC recommended revisions to prevalence and uptake were required.	The submission re-estimated the PBS utilisation based on the results of a new survey of 87 medical practitioners experienced in the treatment of endometriosis, with 55 responders.

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Component	Matter of concern	How this submission addresses it
Duration of treatment	The PBAC noted that the requested restriction did not include a maximum duration of treatment and the approved PI recommends use is limited to 24 months, “with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician”. The revised estimates provided in the pre-PBAC response revised the duration of therapy to 2 years (Para 6.73, March 2024 PSD).	The submission requested the addition of a clinical criterion that, ‘The treatment must not exceed a lifetime maximum of 24 months of therapy’ to address the uncertainty around the duration of treatment and limit the financial risk.
RSA rebate over the caps	The PBAC recommended that an RSA with █████% caps was required to manage the uncertainties in the financial estimates	The submission proposed a rebate of █████% for expenditure over the caps.

Source: p7, p11, p14 of the submission

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RELUGOLIX + ESTRADIOL + NORETHISTERONE ACETATE					
relugolix 40 mg + estradiol 1 mg + norethisterone acetate 500 microgram tablet, 28	NEW MP	1	28	5	Ryeqo
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
	Category / Program: GENERAL – General Schedule				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined)				
	Indication: Endometriosis				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	Patient must have experienced moderate to severe pain associated with endometriosis.				
	Clinical criteria				
	The condition must be visually proven				
	AND				
	Clinical criteria:				
	Patient must have received an inadequate response to, or be intolerant to, previous first line therapies for this condition, including at least one of the following: (i) hormonal contraceptives, (ii) analgesics				
	Clinical criteria:				
	Patient must not have undergone surgery for this condition in the last 3 months; OR				
	Patient must not commence this treatment until 3 months post-surgery				
	AND				
	Clinical criteria:				
	Patient must not have a history of, nor currently have any of the following: (i) osteoporosis, (ii) risk of other metabolic bone disease.				
	AND				
	Clinical criteria:				
	<i>The treatment must not exceed a lifetime maximum of 24 months of therapy</i>				

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	Treatment criteria:
	Must be treated by a specialist medical practitioner with experience in the diagnosis and management of endometriosis
	Population criteria:
	Patient must be pre-menopausal
	AND
	Population criteria:
	Patient must be at least 18 years of age
	Caution: Ryeqo should not be used interchangeably with other GnRH agonists and/or hormonal contraceptives brands due to differences in dose and schedule of treatment
	Prescribing instructions: Assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is recommended at baseline, after the first 52 weeks and 104 weeks of treatment, annually thereafter. Depending on the degree of change in BMD, the benefit and risks of Ryeqo may need to be reconsidered. Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.
Restriction Summary [new 1] / Treatment of Concept: [new 2]	
	Category / Program: GENERAL – General Schedule
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined)
	Indication: Endometriosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have undergone surgery for this condition in the last 3 months
	AND
	Clinical criteria:
	Patient must not have a history of, nor currently have any of the following: (i) osteoporosis, (ii) risk of other metabolic bone disease.
	AND
	Clinical criteria:
	<i>The treatment must not exceed a lifetime maximum of 24 months of therapy</i>
	Treatment criteria
	Must be treated by a specialist medical practitioner with experience in the diagnosis and management of endometriosis
	Population criteria:
	Patient must be pre-menopausal
	Caution: Ryeqo should not be used interchangeably with other GnRH agonists and/or hormonal contraceptives brands due to differences in dose and schedule of treatment
	Prescribing instructions: The prescriber must only request for this treatment phase for the patient if ongoing treatment with this drug is likely to result in an adequate response.
	Prescribing instructions: Details of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) for continuing treatment beyond 6 months if under 41 years of age must be documented in the patient's medical record.

<p>Prescribing instructions: Assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is recommended at baseline, after the first 52 weeks and 104 weeks of treatment, annually thereafter. Depending on the degree of change in BMD, the benefit and risks of Ryeqo may need to be reconsidered. Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.</p>
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Source: Table 3-1 pp14-16 of the submission.

- 3.1 The previous submission requested a DPMQ of \$ [REDACTED]. The current submission requested a DPMQ of \$ [REDACTED] due to changes in mark ups and dispensing fees. The submission did not request a special pricing arrangement.
- 3.2 The submission requested some additional criteria be added to the PBS restriction recommended at the March 2024 PBAC meeting. The submission requested the inclusion of an additional clinical criterion ‘The treatment must not exceed a lifetime maximum of 24 months of therapy’ to manage the uncertainty around the duration of treatment.
- 3.3 Due to this new inclusion, the following amendments to the prescribing instructions were requested:
 - Removing the sentence ‘Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician’; and
 - Revising the bone mineral density by DXA recommendation to ‘...baseline, the first 52 weeks and 104 weeks of treatment’.

4 Population and disease

- 4.1 Endometriosis is a chronic disease that occurs when tissue similar to the lining of the uterus (endometrium tissue) grows outside the uterine cavity. Women with endometriosis typically experience pelvic pain and heavy bleeding during menstruation, while abdominal pain, bloating and fatigue can occur throughout the menstrual cycle. Women with endometriosis are also more likely to have co-existing conditions and chronic diseases, such as uterine fibroids, fibromyalgia, migraine, ovarian cancer, thyroid cancer, cardiovascular diseases and immune disorders (paragraph 4.1, relugolix with estradiol and with norethisterone acetate, PSD March 2024 PBAC meeting).
- 4.2 Ryeqo is a once daily oral FDC containing 40 mg relugolix, 1 mg estradiol (E2) (hemihydrate), and 0.5 mg norethisterone acetate (NETA). It provides hormone therapy to treat endometriosis-associated pain while minimising the risk associated with the therapy. Ryeqo also provides contraception when taken for at least one month. While Ryeqo inhibits ovulation and may cause amenorrhoea, ovulation and menstrual bleeding will return after discontinuing treatment (paragraph 4.9, relugolix with estradiol and with norethisterone acetate, PSD, March 2024 PBAC meeting).

- 4.3 Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. Inhibition of GnRH receptor results in a dose dependent decrease in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. The reduction in FSH concentrations prevents follicular growth and development, thereby reducing the production of estrogen. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes the production of progesterone. The hypoestrogenic state is the main cause of adverse effects, including decreased BMD and vasomotor symptoms (e.g. hot flushes, vaginal dryness and headache). Add-back therapy, usually with E2 and NETA can reduce the adverse effects (paragraph 4.10, relugolix with estradiol and with norethisterone acetate, PSD, March 2024 PBAC meeting).
- 4.4 E2 is a synthetic form of the endogenously produced hormone which is a potent agonist of the nuclear estrogen receptor subtypes. Exogenously administered estradiol alleviates symptoms associated with a hypoestrogenic state such as vasomotor symptoms and BMD loss. NETA is a synthetic progestogen. The addition of a progestogen reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women (paragraph 4.11, relugolix with estradiol and with norethisterone acetate, PSD, March 2024 PBAC meeting).

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

5 Comparator

- 5.1 The March 2024 submission nominated goserelin + add-back therapy as the main comparator, which was accepted by the PBAC. The current submission did not propose a change to the comparator.

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 individuals (9), health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The two organisations were both medical and were the:
- Women's Health and Research Institute of Australia
 - RANZCOG: Royal Australian and New Zealand College of Obstetrics and Gynaecology

- 6.3 The comments described a range of benefits of treatment with relugolix with estradiol (as hemihydrate) and with norethisterone acetate including the delay of surgery and shrinking of fibroids to enable lower risk surgery.
- 6.4 The RANZCOG wrote in support of the timely listing wherever possible of appropriate medications for women's health, including this treatment and to consider patient cost barriers more heavily. This issue of cost as a barrier to access and equity issues for those with endometriosis was raised by multiple contributors including the Women's Health and Research Institute of Australia. The Institute supports this treatment as offering fewer side effects than alternatives, providing choice with an oral mode of delivery, and being a second line option for those that cannot tolerate the other options.

Drug cost/patient/year

- 6.5 The previous submission estimated that the drug cost for Ryeqo would be \$[REDACTED] per year assuming 100% compliance, in the economic models. The current submission did not present an economic model.
- 6.6 The previous submission requested a DPMQ of \$[REDACTED]. The current submission requested a DPMQ of \$[REDACTED] due to changes in mark ups and dispensing fees.
- 6.7 Assuming 100% compliance, the updated drug cost for Ryeqo would be \$[REDACTED] per year (Table 4).

Table 2: Updated comparison of DPMQs for Ryego vs goserelin and nafarelin (plus add-back therapy)

Component	Ryego FDC	Goserelin	Nafarelin (400 mcg)	Nafarelin (800 mcg)	Add-back therapy (Assuming 50/50 split of the below)	
					Levonorgestel 100 mcg + ethinylestradiol 20 mcg ^a	Norethisterone 350 mcg ^b
PBS item code	-	1454M	2962X	5815C	2416E	1967M
PBS item (max qty)	tablets (28)	implant (1)	Nasal spray 200 mcg (60 actuations)	Nasal spray 200 mcg (120 actuations)	Tablets (4x28)	Tables (4x28)
Treatment duration per max qty	28 days	28 days	30 days	30 days	112 days	112 days
DPMQ	\$█	\$213.17	\$124.30	\$222.07	\$19.57	\$19.44
Cost per 28 days	\$█	\$213.17	\$116.01	\$207.27	\$4.89	\$4.86
					Average: \$4.88	
Cost per 6 months (inc. add-back)	\$█	\$1,422.17	\$788.48	\$1,383.66		
Cost of BMD testing yr 1 (MBS item 12321 Fee: \$116.65)	\$116.65	\$0.00	\$116.65	\$116.65		
Cost of implant administration over 6 months (MBS item 14206 \$39.20 + MBS item 23 \$41.40)	\$0.00	\$543.96	\$0.00	\$0.00		
12 months medicine costs: 12 months Ryego vs 6 months goserelin + 6 months nafarelin ^a incl add-back	\$█	\$2,466.57█ (\$1,422.17 + 0.57 x \$788.48 + 0.43 x \$1383.66)				
As above, incl BMD testing and implantation	(\$█+\$116.65)	\$3,127.19 (\$2466.57+ \$543.96 + \$116.65)				
Difference in cost over 1 year		-\$█				

Source: Table 9 - March 2024 Ryego PSD – updated to reflect amended DPMQ and MBS fees

^a Nafarelin cost assumes 57% at 200 mcg twice daily and 43% at 400 mcg twice daily

Estimated PBS usage & financial implications

6.8 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the use of Ryego in female patients aged 18-55 years old. The submission presented a new survey, conducted by Max Power Consulting, of 87 medical practitioners experienced in the treatment of endometriosis, to which there were 55 respondents. The submission provided a copy of the survey questions and results as graphs and descriptive statistics. The submission did not provide any information regarding those surveyed, including possible or actual conflicts of interest.

Table 3: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian female population aged 18 to 55 years	Yr 1: 7,123,000 Yr 2: 7,210,886 Yr 3: 7,284,987 Yr 4: 7,365,305 Yr 5: 7,451,538 Yr 6: 7,542,560 ABS Population Projections; DoH utilisation and cost model workbook	The March 2024 submission estimated use for patients aged 30-55 years old. DUSC considered limiting the eligible population to those aged between 30 to 55 years in the financial estimates was not appropriate as it would substantially underestimate the patient population and advised that the eligible population should be revised to those aged 18 years or over. The revised financial estimates provided in the pre-PBAC response revised the eligible population to patients aged 18-55 years. The current submission estimated use for patients aged 18-55 years old which was appropriate.
Prevalence of endometriosis	12%, March 2024 PSD par. 6.80 (Appendix 1)	This was appropriate. The PBAC (March 2024) requested a revised prevalence of 12% to better reflect prevalence in the broader age group as there is evidence that the prevalence rate is lower in younger patients and the assumption of 14% was based on the 44-49 age group. AIHW cites the results of a US online survey (Fuldeore & Soliman 2017) reporting a prevalence of diagnosed endometriosis of 6.1% in patients aged 18-49.
Visually proven endometriosis and experiencing moderate to severe pain	57.94%, Commissioned market research (Appendix 3)	The March 2024 submission estimated 30% of patients experience moderate to severe pain. This was revised to 50% in the pre-PBAC response, however the PBAC requested it be revised back to 30%. The PBAC considered this estimate was uncertain and the increase was not well-justified. The PBAC agreed with the submission that gynaecologists' perceptions would be skewed towards estimating a higher proportion. The current submission has estimated 57.94% of patients have visually proven endometriosis and experience moderate to severe pain, based on the new survey presented in the submission. The submission provided the mean result for each question for all responders to the survey and did not note whether there were differences in the results for different specialities. Of the responders, 79% reported they were gynaecology or obstetrics and gynaecology specialists.
Also meet all the other PBS criteria including (a) no surgery in last 3 months, (b) no history of or current have osteoporosis and/or risk of other metabolic bone disease and (c) have response inadequately to or have been intolerant to previous first-line therapies including at least one of the following (i) hormonal contraceptives, (ii) analgesics.	39.60%, Commissioned market research (Appendix 3)	The March 2024 submission estimated the proportion of patients who failed or for whom first line treatment was inadequate to be 50% in year 1, increasing to 63.8% in year 6. The current submission has replaced this assumption with an estimate of the proportion of patients who meet all other PBS criteria, from the market survey described above.

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Parameter	Value applied and source	Comment
Uptake rate (cumulative)	<p>Yr 1: █████ %</p> <p>Yr 2: █████ %</p> <p>Yr 3: █████ %</p> <p>Yr 4: █████ %</p> <p>Yr 5: █████ %</p> <p>Yr 6: █████ %</p> <p>Commissioned market research & sponsor assumptions</p>	<p>The uptake assumptions in the March 2024 submission (Table 21) were based on the global market research survey for patients aged 30-55 years. Prescribing of Ryeqo would be expected to be lower in younger patients, which would reduce the overall treatment uptake. In addition, the PBAC noted that the uptake rates were applied to the prevalent population such that the cumulative uptake by year 6 was greater than █████%. The PBAC considered that the cumulative uptake over 6 years would be no higher than █████% of eligible patients (para 6.80, March 2024 PSD).</p> <p>The current submission used the market survey discussed above to claim that the mean proportion of patients who would be prescribed Ryeqo was 71.1%. The submission stated that this proportion was broadly aligned with the uptake from the previous survey noted by the DUSC, and that the increase in uptake rate is likely due to the greater awareness of Ryeqo since the previous survey was undertaken. The survey questions provided in the submission note that responders were asked how many eligible patients they would prescribe Ryeqo. The submission did not provide any information regarding possible or actual conflicts of interest of those surveyed, and it did not ask if they were already familiar with Ryeqo. If clinicians surveyed were involved in the clinical trial or are familiar with Ryeqo, this may have overestimated the uptake.</p> <p>The submission noted that the patient organisation for those living with endometriosis and pelvic pain, QENDO, recently conducted a national survey, and noted that 95% of patients would utilise new treatments if available on the PBS (Appendix 4 of the submission). The methods and questions of this survey were not provided. It is understandable that a high proportion of responders would agree that they would utilise new treatments available on the PBS if they were not given any further information regarding side effects or the number of treatments allowed in their lifetime. However it is unlikely that the uptake of Ryeqo would be as high as 95% in practice.</p> <p>The submission stated that these data support the use of a cumulative uptake rate that is substantially higher than that suggested by the PBAC.</p> <p>The submission used the stated cumulative uptake rates to calculate the number of treated patients from the number of eligible patients. The number of treated patients in previous years was then subtracted to determine the number of new patients in each year. It was appropriate to exclude previously treated patients from the estimate of new patients as the proposed PBS restriction limits treatment to 24 months lifetime therapy, however the resulting cumulative uptake in year 6 was █████%.</p>

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Parameter	Value applied and source	Comment
Compliance rate	80%, March 2024 PSD par. 6.76 Table 10 (Appendix 1)	Appropriate. The March 2024 submission applied a compliance rate of 80%. The PBAC (March 2024) considered this was underestimated but did not request it be changed. Overall compliance in the SPIRIT trials was high 97.4-99% for Ryeqo group to Week 24 and cumulative compliance >98% in all treatment groups to Week 104 in SPIRIT Extension. This assumption was also inconsistent with the modelled economic evaluation, which assumed 100% compliance for Ryeqo. DUSC considered compliance could be high due to the ease of administration and a highly motivated eligible population. However, DUSC considered compliance could also be lower in clinical practice where patients are non-responsive to treatment because the cause of pain is not endometriosis.
Duration of treatment	2 years, Sponsor proposed	The March 2024 submission applied a treatment duration of one year which DUSC considered was likely an underestimate. The revised estimates provided in the pre-PBAC response revised the duration of therapy to 2 years. The current submission included wording in the proposed PBS restriction to limit treatment to two years, and has applied a treatment duration of two years in the estimates. This was appropriate, however as the PI does allow longer duration of therapy conditional on stability of DXA, there may still be a risk of use beyond two years outside the PBS restriction.
MBS costs	MBS item number 12321	The PI recommends that clinicians perform a dual X-ray absorptiometry (DXA) scan before commencing treatment and one year after commencing treatment in at risk patients. The March 2024 submission did not include any assessment of costs to the MBS in the financial estimates (Para 6.83, March 2024 PSD). The PBAC advised that costs for annual testing of patients up to 40 years of age, while on treatment, should be included (Para 7.14, March 2024 PSD). The current submission estimates costs associated with increased bone densitometry scans (MBS item 12321), and decreased costs associated with bone densitometry scans, hormone or living tissue implantation by cannula (MBS item 14206), and professional attendance by a GP between 6 and 20 mins (MBS item 23). The submission noted the fee for bone densitometry scans was \$112.73, however from 1 July 2024 the fee was \$116.65, these fees were updated in Table 4.

Source: Table 10, March 2024 PSD, pp42-44, Tables 2-1, 2-2, 2-3, 2-8, 2-9 pp4-10 of the submission, Section 4 spreadsheet '7. Net changes – MBS' of the submission

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients initiating	█ ¹	█ ¹	█ ²	█ ¹	█ ³	█ ¹
Number of scripts dispensed ^a	█ ⁴	█ ⁵	█ ⁶	█ ⁵	█ ⁷	█ ⁷
Estimated financial implications of Ryego						
Cost to PBS/RPBS less copayments	\$█ ⁸	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ¹⁰	\$█ ¹⁰
Estimated financial implications for {other medicines}						
Cost to PBS/RPBS less copayments	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁸	\$█ ¹²	\$█ ⁹	\$█ ⁹	\$█ ¹⁰	\$█ ¹³
Net cost to MBS	\$█ ¹⁴	\$3█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Previous submission March 2024						
Net cost to PBS/RPBS	\$█ ¹⁵	\$█ ¹⁶	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ¹⁷
Previous submission March 2024 – pre-PBAC Response						
Net cost to PBS/RPBS	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹
Previous submission March 2024 – PBAC requested revisions						
Net cost to PBS/RPBS (indicative)	\$█ ¹⁴	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁸	\$█ ¹⁸

Source: Tables 2-8, 2-10, 2-13 pp10-13 of the submission, '4b. Impact - affected (pub)' and '5. Impact – net', Section 4 spreadsheet
 Ratified PBAC minutes relugolix with estradiol and with norethisterone acetate March 2024

^a Assuming 10.44 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

- ¹ 20,000 to < 30,000
- ² 30,000 to < 40,000
- ³ 10,000 to < 20,000
- ⁴ 200,000 to < 300,000
- ⁵ 500,000 to < 600,000
- ⁶ 600,000 to < 700,000
- ⁷ 400,000 to < 500,000
- ⁸ \$40 million to < \$50 million
- ⁹ \$100 million to < \$200 million
- ¹⁰ \$80 million to < \$90 million
- ¹¹ net cost saving
- ¹² \$90 million to < \$100 million
- ¹³ \$70 million to < \$80 million
- ¹⁴ \$0 to < \$10 million
- ¹⁵ \$20 million to < \$30 million
- ¹⁶ \$30 million to < \$40 million
- ¹⁷ \$50 million to < \$60 million
- ¹⁸ \$10 million to < \$20 million

Table 5: Comparison of previous and current submission

	Original submission	Pre-PBAC response	PBAC	Current submission
Australian women	Aged 30-55 years	Aged 18-55 years	Aged 18-55 years	Aged 18-55 years
% diagnosed with endometriosis	14%	14%	12%	12%
% with moderate to severe pain	30%	50%	30%	57.94%
% failed or for whom first line treated was inadequate	Year 1: 50.00% Year 2: 52.50% Year 3: 55.13% Year 4: 57.88% Year 5: 60.78% Year 6: 63.80%	Year 1: 50.00% Year 2: 52.50% Year 3: 55.13% Year 4: 57.88% Year 5: 60.78% Year 6: 63.80%	Year 1: 50.00% Year 2: 52.50% Year 3: 55.13% Year 4: 57.88% Year 5: 60.78% Year 6: 63.80%	39.6%
Overall eligibility	15% to 19.14%	25% to 31.9%	15% to 19.14%	22.94%
Uptake rates	Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████%	Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████%	PBAC revised: Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████% PBAC cumulative uptake: Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████%	Cumulative rates stated in the main body: Yr 1: █████% Yr 2: █████% Yr 3: █████% Yr 4: █████% Yr 5: █████% Yr 6: █████% Rates applied in the Section 4 workbook (cumulative including new patients) Yr 1: █████% (█████%) Yr 2: █████% (█████%) Yr 3: █████% (█████%) Yr 4: █████% (█████%) Yr 5: █████% (█████%) Yr 6: █████% (█████%)
Duration of treatment	1 year	2 years	2 years	2 years

Source: Ratified Minutes par 6.76 - 6.80, 5.18 DUSC ADV.4-7 (Appendix 1)

6.9 The total cost to the PBS/RPBS of listing Ryego was estimated to be \$80 million to < \$90 million in Year 6, and a total of \$500 million to < \$600 million in the first 6 years of listing.

6.10 The submission relied on the results from commissioned market research to re-estimate the number of treated patients. The submission provided a copy of the survey questions and results for each question separately as graphs and descriptive statistics. The five questions asked by the survey were:

- How many pre-menopausal women aged at least 18 years old, with endometriosis are currently under your care.
- Of these patients, how many have visually proven endometriosis and experience moderate to severe pain from endometriosis.
- Of these patients, how many also meet all of the following criteria

- Have not had surgery in the last three months
 - Do not have a history of (or currently have) either osteoporosis and/or risk of other metabolic bone disease
 - Have responded inadequately to, or have been intolerant to, previous first line therapies for endometriosis including at least one of the following (i) hormonal contraceptives, (ii) analgesics
 - And of the above patients how many of these would you prescribe Ryeqo to
 - Please tell us your specialty. Options were:
 - Gynaecology
 - Obstetrics and gynaecology
 - Gynaecological oncology
 - General Practice
 - Other (please specify)
- 6.11 The questions appear reasonable, however the submission did not provide any information regarding possible or actual conflicts of interest of those surveyed, and it did not ask if they were already familiar with Ryeqo. In recommending Ryeqo, PBAC (March 2024) agreed with the submission that gynaecologists' perceptions would be skewed towards estimating a higher proportion of patients experiencing moderate to severe pain. The submission provided the mean result for each question for all responders to the survey and did not note whether there were differences between results for different specialties.
- 6.12 The submission noted that the patient organisation for those living with endometriosis and pelvic pain, QENDO, recently conducted a national survey, which noted that 95% of patients would utilise new treatments if available on the PBS (Appendix 4 of the submission). The results of this survey were provided as a four page summary, including the result that 95% of patients would utilise new treatments if available on the PBS. The submission did not include any details about the methods or the questions asked during the survey. It is likely that a high proportion of responders would agree that they would utilise new treatments available on the PBS if they are not given any further information regarding the number of treatments they would be allowed in their lifetime, however it is unlikely that the uptake of Ryeqo would be as high as 95% in practice.
- 6.13 The submission estimated the net cost to PBS/RPBS to be \$500 million to < \$600 million over 6 years, which was a substantial increase from the PBAC revised estimate of \$90 million to < \$100 million over 6 years. The increase of 4-8% in overall eligibility of prevalent patients contributed to the increased estimates, but the difference in financial estimates is largely due to the increased uptake rates applied.

- 6.14 The submission has claimed cost offsets from goserelin, nafarelin and levonorgestrel plus ethinylestradiol, and did not include cost offsets from analgesics. The submission noted that it was assumed that, “11% of the total eligible population for Ryego would no longer use goserelin/nafarelin. The estimate of 11% was based on the PBAC’s comment that ‘...the offsets should be reduced to be consistent with the current PBS usage of GnRH therapy for endometriosis and hence to account for additional patients accessing treatment.’ (Paragraph 6.82, relugolix with estradiol and with norethisterone acetate, PSD, March 2024 PBAC meeting). Specifically, applying 11% to the treated population gives a total number of prescriptions for goserelin that aligns with those dispensed for endometriosis through the PBS. Noting that the original submission estimated that only 15% of all PBS prescriptions for goserelin were for endometriosis”. (Section 4 spreadsheet, ‘4a. Scripts – affected, rows 431 to 436). As the PBS listing for goserelin is a Restricted Benefit for carcinoma of the prostate, breast cancer, endometriosis, and anticipated premature ovarian failure, it is unclear how the submission determined how many prescriptions of goserelin were dispensed for endometriosis.
- 6.15 At year 6, the estimated number of initiating patients was 20,000 to < 30,000 and the net cost to the PBS would be \$70 million to < \$80 million.

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

Quality Use of Medicines

- 6.16 No quality use of medicines issues were identified in the submission and no QUM activities were proposed in the submission. DUSC commented that patients should understand the implications of BMD loss before initiating Ryego treatment.
- 6.17 DUSC also noted the submission did not propose a treatment pathway for patients following 24 months of Ryego treatment, given Ryego only manages the symptoms of pain.
- 6.18 The submission did not provide any further information regarding QUM.

Financial Management – Risk Sharing Arrangements

- 6.19 The PBAC (March 2024) advised that additional revisions to prevalence and uptake were required as well as a risk sharing arrangement (RSA) with % caps to manage the uncertainties in the financial estimates.
- 6.20 The submission noted that the PBAC’s proposed expenditure caps ensures that all the financial risk of a mean treatment duration longer than 2 years is carried by the sponsor, and stated that this is a level of risk that the sponsor cannot accept as it jeopardizes the long-term commercial viability of Ryego as well as the company. The submission suggested it would be appropriate for the sponsor and the PBAC to agree on a likely mean duration of treatment and revise the expenditure caps accordingly. However, the submission noted there are currently no clinical trial data or real-world evidence globally that may be used to determine a reasonable estimate of the mean

duration of treatment. The sponsor therefore proposed an additional clinical criterion be added to the PBS restriction to limit lifetime treatment to 24 months, and that the rebate beyond the caps be changed from 1% to 2%.

7 PBAC Outcome

- 7.1 The PBAC did not revise its March 2024 advice in relation to the utilisation estimates of relugolix with estradiol and with norethisterone. The PBAC considered that the submission did not provide sufficient justification to support the proposed financial estimates and RSA.
- 7.2 The PBAC noted that the submission estimated the net cost to the PBS/RPBS to be \$500 million to < \$600 million over 6 years, which was a substantial increase from the March 2024 PBAC recommendation of \$90 million to < \$100 million over 6 years. The increase of 4-8% in overall eligibility of prevalent patients contributed to the increased estimates, but the difference in financial estimates was largely due to the increased uptake rates applied. The PBAC noted the clinician survey presented by the submission as justification for the changes in the utilisation inputs was unreliable. The PBAC reiterated that there was a high level of uncertainty in relation to the prevalence and uptakes estimates, however the submission's proposed estimates appeared to be substantially overestimated. The PBAC considered that the utilisation estimates and consequent subsidisation caps recommended at its March 2024 meeting should not be increased.
- 7.3 The PBAC noted the submission's request that the rebate beyond the RSA caps be changed from 1% to 2%. The PBAC considered this request was not appropriate as the submission did not address the cost-effectiveness of Ryeqo beyond 2 years of treatment and the risk of use outside the restriction remained.
- 7.4 The PBAC accepted the submission's proposed additional clinical criterion for the PBS restriction to limit treatment to a lifetime maximum of 24 months. The PBAC advised that the restriction changes detailed in Section 3 should be applied to the March 2024 recommended listing.
- 7.5 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Advice Provided

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.

10 Sponsor's Comment

Gedeon Richter is disappointed that the PBAC has not accepted our financial estimates, which Gedeon Richter believes are supported by the survey data and reflect the anticipated uptake. Gedeon Richter remains committed to working closely with the PBAC to address any concerns and find a solution to make Ryeqo available on the PBS for patients with endometriosis as soon as possible.