7.11 RIMEGEPANT, Tablet (orally disintegrating) 75 mg, Nurtec® ODT, PFIZER AUSTRALIA PTY LTD.

1 Purpose

1.1 The early re-entry resubmission requested a General Schedule Authority Required (STREAMLINED) listing of rimegepant for the treatment of adult patients with migraine who have not responded adequately, are intolerant or contraindicated to analgesics and at least two selective 5-hydroxytryptamine receptor agonists (triptans).

1.2 The resubmission was based on the PBAC decision to not recommend rimegepant for this indication in July 2023. This resubmission addressed the issues raised by PBAC; see Table 1 below.

Table 1: Issues raised by PBAC from the July 2023 submission for rimegepant

Matter of concern	Response	Addressed?
Revisions to the restriction including: • combining the initial, continuing and grandfather restrictions under a single treatment phase; and • amending the restriction to allow prescribing of rimegepant by general practitioners.	The early re-entry resubmission: • proposed a single treatment phase; and • removed the requirement for specialist prescribing.	 Yes Yes
Revisions to the economic model including: • using data from the mITT analysis rather than the *post hoc*, pooled subgroup analysis for the modelled outcome of pain relief at 2 hours; • reducing the time horizon from 5 years to 1 year; • adjusting the utility values to apply a baseline utility that was based on MSQ data and then adjusting the utilities from Stafford et al (2012) using the multiplicative approach; • transitioning patients who discontinue treatment with rimegepant to the placebo/BSC non-responder arm, rather than the placebo/BSC responder arm; and • reducing the price at the DPMQ level to result in an ICER that was equivalent to that in the submission (i.e. $[redacted][1] per QALY).	The early re-entry resubmission: • continued to apply data from the *post hoc*, pooled subgroup analysis; • applied a time horizon of 3 years; • adjusted the utility values as requested; • transitioned patients who discontinued rimegepant as requested; and • reduced the price at the DPMQ level to result in an ICER of $[redacted][2] per QALY.	 No Partially Yes Yes Partially
Provide financial estimates based on the utilisation estimates presented in the submission and using the revised price obtained from the economic analysis.	The early re-entry resubmission presented estimates in which the utilisation of rimegepant was substantially increased, in addition to including the revised price obtained from the economic analysis.	No
Provision of a RSA to manage the uncertainties in rimegepant eligibility, uptake and use.	The early re-entry submission proposed a three tier RSA based on the revised financial estimates.	No

Source: compiled from the July 2023 rimegepant Public Summary Document and the March 2024 early re-entry resubmission
BSC = best supportive care; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; mITT = modified intention to treat; MSQ = Migraine Specific Quality of Life Questionnaire; QALY = quality adjusted life year; RSA = risk-sharing arrangement
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*
[2] *$25,000 to < $35,000*

2 Background

2.1 Rimegepant was registered on the Australian Register of Therapeutic Goods on 27 July 2023 and is indicated for:

- acute treatment of migraine with or without aura in adults; and
- prophylactic treatment of episodic migraine in adults who have at least 4 migraine attacks per month.

2.2 The key components from the previous submission are presented below.

Table 2: Key components of the clinical issues

Component	Description
Population	Adults with moderate to severe acute migraine attacks who inadequately responded to at least 2 triptans, or are intolerant or contraindicated to triptans, and require treatment for not more than eight acute migraine attacks of moderate to severe intensity per month[a]
Intervention	Rimegepant 75 mg oro-dispersible tablet
Comparator	Placebo (as a proxy for best supportive care as last line treatment option after ≥ 2 failed triptans)
Outcomes	Pain relief at 2 hours Adverse events and serious adverse events
Clinical claim	Rimegepant is superior to placebo in terms of efficacy. Rimegepant is non-inferior to placebo in terms of safety.

Source: Table 1.1.1, p2 of the submission.

[a] The restriction also included inadequate response, intolerance or a contraindication to analgesics.

3 Requested listing

3.1 The restriction proposed in the resubmission included the following revisions requested by the PBAC in July 2023:

- The requirement for prescribing by a specialist was removed as the PBAC determined that prescribing by a general practitioner was appropriate;
- The continuing and grandfather restrictions were removed as neither were required for an acute treatment;
- The addition of the clinical criterion to monitor for medication overuse headache; and
- The addition of the administrative advice stating that rimegepant is not PBS subsidised for the prophylaxis of migraine.

3.2 Secretariat additions are in italics and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
RIMEGEPANT					
Rimegepant, 75 mg, orally disintegrating tablet, 2	Published: $[redacted] Effective: $[redacted]	1	2	1	Nurtec ODT
Rimegepant, 75 mg, orally disintegrating tablet, 8	Published: $[redacted] Effective: $[redacted]	1	8	2	

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ Authority Required (STREAMLINED)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: This drug is not PBS-subsidised for prophylaxis of migraine
Episodicity: blank
Severity: blank
Condition: blank
Indication: Migraine attack

Treatment criteria:
Patient must not be undergoing concurrent treatment with the following PBS benefits listed for treatment/prevention of migraine: (i) botulinum toxin type A, (ii) calcitonin gene-related peptide (CGRP) inhibitor
AND
Clinical criteria:
Patient must *not* have experienced ~~not~~ more than 8 acute migraine attacks of moderate to severe intensity per month, over a period of at least 3 months prior to commencing treatment with this drug for this condition
AND
Clinical criteria
Patient must have experienced at least one of (i) an inadequate response, (ii) intolerance, (iii) a contraindication to both of (a) analgesics, (b) at least two of selective 5-hydroxytryptamine (5-HT) receptor agonist medications (triptans) prior to commencing treatment with this drug for this condition
AND
Clinical criteria:
Patient must continue to achieve an adequate response to this drug for this condition to receive continuing supply
AND
Clinical criteria
Patient must be appropriate*ly* managed by their practitioner for medication overuse headache
Population criteria:
Patient must be at least 18 years of age
Prescribing instructions: Selective 5-hydroxytryptamine receptor agonists (triptans) medications are sumatriptan, eletriptan, zolmitriptan, naratriptan or rizatriptan
Prescribing instructions: *[For 2 tablet pack] For use as initial supply only* *[For 8 tablet pack] For use as continuing supply only*

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item. The PBAC recalled that in July 2023 there was a sponsor hearing for this item. The clinician discussed the unmet need for more effective acute treatments for migraine and described the limitations of currently available therapies.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (9) via the Consumer Comments facility on the PBS website for this resubmission. The PBAC recalled that for the July 2023 submission input was received from individuals (45) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals and the consumer organisations, Migraine & Headache Australia, the Australian and New Zealand Headache Society and Pain Australia,

strongly supported the submission. They described the need for new, effective and safe treatments for acute migraine, the potential benefits of rimegepant in relieving acute migraine pain and frequency. The comments also described the effects of migraines on quality of life, including the debilitating effect of migraines and a decreased ability to work, study and socialise. The PBAC noted that a number of consumer comments provided related to the chronic use of rimegepant.

4.3 The PBAC recalled the advice received from Migraine Australia which provided a detailed description of the impact of migraine and the current available therapies. The advice also highlighted the importance of the availability of alternate options for the treatment of acute migraine prophylaxis and clarifying the likely use of rimegepant in clinical practice. The PBAC specifically noted the advice that the use of rimegepant may improve the quality of life of migraine sufferers.

Clinical claim

4.4 The July 2023 submission described rimegepant as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo in adults with moderate to severe migraine attacks who inadequately responded to at least two triptans or who are intolerant or contraindicated to triptans.

4.5 Based on the results of the analyses presented in the submission, in July 2023 the PBAC considered that a single dose of rimegepant was superior compared to BSC in terms of treating an acute migraine. The PBAC, noting that no longer term efficacy data were presented in the submission, considered that the long-term treatment effect of rimegepant was uncertain (paragraph 7.8, rimegepant public summary document (PSD), July 2023).

4.6 In terms of safety, in July 2023 the PBAC noted that although slightly higher rates of adverse events were reported by patients who received rimegepant compared to those who received placebo, rimegepant was well tolerated. Overall, the PBAC considered that rimegepant was non-inferior compared to BSC in terms of safety (paragraph 7.9, rimegepant PSD, July 2023).

4.7 The PBAC's consideration of the comparative clinical effectiveness and safety remain unchanged from July 2023.

4.8 The PBAC recalled that for every 100 patients treated with rimegepant in comparison with placebo for a single migraine episode, an additional 14 to 33 patients would experience pain relief at two hours (paragraph 6.37, rimegepant PSD, July 2023 PBAC meeting). The PBAC considered the clinical benefit of rimegepant was modest.

Economic analysis

4.9 In July 2023, the PBAC considered that the base case incremental cost-effectiveness ratio (ICER) presented in the submission ($15,000 to < $25,000 per QALY) was

optimistic (paragraph 7.10, rimegepant PSD, July 2023). The PBAC suggested four changes to the model which increased the ICER to $45,000 to < $55,000 per QALY:

- The efficacy inputs were based on the *post hoc*, pooled subgroup analysis of the secondary outcome, pain relief at two hours. The PBAC considered that the use of the *post hoc*, pooled subgroup analyses was not adequately justified and data from the mITT analysis should be used.
- As the assumption that the efficacy of rimegepant would be maintained over the 5-year time horizon was highly uncertain given the trial results related to a single migraine attack, the PBAC considered that a 1-year time horizon would be more appropriate.
- The model was sensitive to the utility values applied. The PBAC noted although the results of the Migraine Specific Quality of Life (MSQ) questionnaire collected from BHV3000-201 could not be used to estimate the impact of a migraine attack, they could be used to estimate an alternate baseline utility. The PBAC considered that the approach which applied a baseline utility that was based on the MSQ data and then adjusted using the utilities from Stafford et al (2012) and the multiplicative approach was the most appropriate.
- The model assumed that patients who discontinued treatment with rimegepant transitioned into the placebo/BSC responder arm, which resulted in an ongoing QALY benefit per migraine. The PBAC considered that it would be more appropriate if these patients transitioned to the placebo/BSC non-responder arm as patients who received rimegepant were required to have previously failed analgesics and at least two triptans and were therefore unlikely to respond to placebo/BSC.

4.10 The PBAC considered that if the above changes were made to the model, then rimegepant would be cost effective if the price was adjusted to result in a base case ICER which was equivalent to that presented in the July 2023 submission (i.e. $15,000 to < $25,000 per QALY). The PBAC noted this resulted in a price per tablet at the DPMQ level of approximately $ to $ and considered this to be a more plausible cost-effective price compared to the requested price per tablet ($ to $) (paragraph 7.11, rimegepant PSD, July 2023).

4.11 As noted in Table 1, the resubmission accepted two of the suggested changes to the model (baseline utility value and rimegepant discontinued health state) and proposed an approximate % reduction to the effective DPMQ of rimegepant (2-pack was reduced from $ to $; 8-pack was reduced from $ to $). These changes resulted in an ICER of $25,000 to < $35,000 per QALY and a cost per tablet of between $ and $; see Table 3.

Table 3: Results of the economic model and the changes requested by PBAC in July 2023

	July 2023 submission	July 2023 PBAC suggested changes	March 2023 Early re-entry resubmission
Efficacy values	2-hour pain relief – *post hoc*, pooled subgroup Rimegepant = 69.3% BSC = 36.7%	2-hour pain relief – mITT Rimegepant = 57.9% BSC = 43.8%	2-hour pain relief – *post hoc*, pooled subgroup Rimegepant = 69.3% BSC = 36.7%
Time horizon	5 years	1 year	3 years
Baseline utility values	Stafford (2012) Baseline value = 0.87	Stafford (2012) utility values adjusted using the MSQ data from BHV3000-201 and the multiplicative approach. Baseline value = 0.7076	Stafford (2012) utility values adjusted using the MSQ data from BHV3000-201 and the multiplicative approach. Baseline value = 0.7076
Rimegepant discontinued health state, QALH	Placebo/BSC responder arm QALH = 37.59	Placebo/BSC non-responder arm QALH = 28.68	Placebo/BSC non-responder arm QALH = 28.68
ICER using July 2023 effective DPMQs: 2-pack = $[redacted] 8-pack = $[redacted]	$[redacted]*[1] per QALY	$[redacted]*[2] per QALY	$[redacted][3] per QALY
ICER using March 2024 proposed effective DPMQs: 2-pack = $[redacted] 8-pack = $[redacted]	$[redacted][1] per QALY	$[redacted][4] per QALY	**$[redacted][3] per QALY**

Source: Table 3, p10 of the early re-entry submission; and Excel workbook – PBAC Rimegepant in Acute Migraine CEA

BSC = best supportive care; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; mITT = modified intention to treat; MSQ = Migraine Specific Quality of Life Questionnaire; QALH = quality adjusted life hours; QALY = quality adjusted life year

* ICERs differ slightly to July 2023 rimegepant PSD as the DPMQs are based on July 2023 PBS fees and mark-ups, rather than July 2022 fees and mark-ups

The redacted values correspond to the following ranges:

[1] *$15,000 to < $25,000*

[2] *$45,000 to < $55,000*

[3] *$25,000 to < $35,000*

[4] *$35,000 to < $45,000*

4.12 The resubmission acknowledged that the proposed ICER of $25,000 to < $35,000 per QALY was higher than that requested by the PBAC in July 2023, but stated that the lowest sustainable price for rimegepant has been offered. The resubmission stated that the PBAC's concern that using the *post hoc*, pooled subgroup analysis may increase the risk of bias as the effects of randomisation was not valid. The resubmission noted that of the 3,507 patients in the mITT population, 48.7% (n=1,677) were naïve to triptans, whilst 64.8% (n=2,272) had no history of discontinued triptans. Therefore, using the mITT population for decision making biases the economic evaluation in favour of the triptan-naïve and triptan-responding populations, which does not align with the proposed PBS restriction. Further, the resubmission provided additional results comparing the prespecified subgroup (for which the reason for treatment failure was efficacy and patients had to fail all routes of administration for a molecular entity) and the *post hoc*, pooled subgroup (for which the reason for treatment failure was efficacy or intolerance and patients did not need to fail on all routes of administration) for three of the secondary outcomes (Table 4). The

resubmission stated that as the analyses had similar point estimates and statistical significance, the concerns about the risk of bias have been addressed.

Table 4: Primary and secondary outcomes for the *post hoc*, pooled subgroup analyses and the prespecified pooled subgroup analysis from the Phase 3 trials (BHV3000-301-302-303)

	***Post hoc*, pooled subgroup analysis**			**Prespecified, pooled subgroup analysis**		
	RIM n/N (%)	**PBO n/N (%)**	**RD (95% CI; p-value)**	**RIM n/N (%)**	**PBO n/N (%)**	**RD (95% CI; p-value)**
Primary endpoints						
Pain freedom at 2 hours post-dose	30/148 (20.3%)	18/177 (10.2%)	**9.8 (2.0, 17.5; p=0.0131)**	15/78 (19.2%)	10/104 (9.6%)	9.6 (-0.8, 20.0; p= 0.0702)
Freedom from MBS at 2 hours post-dose	64/148 (43.2%)	38/177 (21.5%)	**21.5 (11.6, 31.4; p<0.0001)**	29/78 (37.2%)	19/104 (18.3%)	**18.9 (5.9, 32.0; p=0.0045)**
Secondary endpoints						
Pain relief at 2 hours post dose	103/148 (69.6%)	65/177 (36.7%)	**32.9 (22.6, 43.1; p<0.0001)**	53/78 (67.7%)	38/104 (36.5%)	**31.4 (17.6, 45.3; p<0.0001)**
Functional disability at 2 hours post dose	55/148 (37.0%)	28/177 (15.8%)	**21.1 (11.7, 30.5; p<0.0001)**	27/78 (34.2%)	16/104 (15.4%)	**18.8 (6.5, 31.1; p=0.0028)**
Sustained pain relief 2-48 hours post-dose	70/148 (47.1%)	32/177 (18.0%)	**29.1 (19.3, 38.9; p<0.0001)**	37/78 (44.4%)	19/104 (18.1%)	**26.4 (13.4, 39.3; p<0.0001)**

Source: Table 5, p13 of the early re-entry resubmission
CI = confidence interval; MBS = most bothersome symptom; PBO = placebo; RD = risk difference; RIM = rimegepant
Bold = nominal statistical significance (p<0.05)
Blue shading = results previously seen by the PBAC

4.13 The PBAC previously considered that the maintenance of the efficacy of rimegepant was highly uncertain over the 5-year time horizon as the pivotal studies (BHV3000-301-302-303) were based on a single migraine attack. The resubmission highlighted that patients who achieved a response in the single attack studies then entered the long-term safety study (BHV3000-201), in which the probability of discontinuing treatment due to adverse events, lack of efficacy or withdrawal by the patient was 9.7% at 52 weeks. The resubmission stated that this demonstrated that patients continued to receive rimegepant and that it was effective. The resubmission considered that the application of a 3-year time horizon in the revised base case was conservative. Application of a 1-year time horizon increased the ICER from $25,000 to < $35,000 per QALY to $25,000 to < $35,000 per QALY.

Estimated PBS usage and financial implications

4.14 In July 2023, the PBAC, noting the large variability in the sensitivity analyses for the financial estimates, considered that the utilisation estimates included in the submission may form a reasonable basis for an RSA to manage the uncertainties in rimegepant eligibility, uptake and use (paragraph 7.12, rimegepant PSD, July 2023). Further, the PBAC stated that an early re-entry resubmission should provide revised financial estimates that were based on the utilisation estimates provided in Table 16

of the July 2023 PBAC PSD (paragraph 7.14, rimegepant PSD, July 2023) and incorporating the revised price obtained for the economic analysis.

4.15 The resubmission has provided revised financial estimates in which a number of the utilisation inputs were substantially increased. Table 5 presents a comparison of the utilisation inputs.

Table 5: Comparison of utilisation inputs from July 2023 to March 2024

Data	July 2023 value	March 2024 value	Comment
Australian population: adults ≥ 18 years (Year 1)	21,411,852	21,411,852	-
Prevalence of migraine	14.5%	14.5%	-
% of migraine that is episodic	90%	90%	-
% of patients with episodic migraine who received a pharmacological treatment	29%	56.6%	The resubmission noted that Table 15 of the July 2023 PSD states that the ESC considered that the estimate of 29% was likely largely underestimated.
% of patients with episodic migraine who failed ≥ 2 triptans	9.3%	12.4%	The resubmission noted that Table 15 of the July 2023 PSD states that the estimate of 9.3% was uncertain.
% of patients who have ≤ 8 migraine attacks per month (acute)	97.5%	97.5%	-
Uptake rate of rimegepant	Year 1: [redacted] % Year 2: [redacted] % Year 3: [redacted] % Year 4: [redacted] % Year 5: [redacted] % Year 6: [redacted] %	Year 1: [redacted] % Year 2: [redacted] % Year 3: [redacted] % Year 4: [redacted] % Year 5: [redacted] % Year 6: [redacted] %	The resubmission noted that Table 15 of the July 2023 PSD states that the ESC considered that the uptake rates were likely underestimated.
Total number of patients treated	Year 1: [redacted][1] Year 2: [redacted][2] Year 3: [redacted][3] Year 4: [redacted][4] Year 5: [redacted][5] Year 6: [redacted][6]	Year 1: [redacted][3] Year 2: [redacted][6] Year 3: [redacted][7] Year 4: [redacted][7] Year 5: [redacted][7] Year 6: [redacted][7]	-
Number of scripts dispensed	Year 1: [redacted][3] Year 2: [redacted][7] Year 3: [redacted][7] Year 4: [redacted][8] Year 5: [redacted][9] Year 6: [redacted][10]	Year 1: [redacted][8] Year 2: [redacted][10] Year 3: [redacted][11] Year 4: [redacted][12] Year 5: [redacted][13] Year 6: [redacted][13]	-
Net budget impact using March 2024 proposed effective DPMQs: 2-pack = $[redacted] 8-pack = $[redacted]	$[redacted][14]	$[redacted][15]	-

Source: Table 7, p16 of the early re-entry resubmission

DPMQ = dispensed price for maximum quantity

* Total cost differs slightly to July 2023 rimegepant PSD as the DPMQs are based on July 2023 PBS fees and mark-ups, rather than July 2022 fees and mark-ups

The redacted values correspond to the following ranges:

[1] *10,000 to < 20,000*

[2] *20,000 to < 30,000*

[3] *40,000 to < 50,000*

[4] *50,000 to < 60,000*

[5] *60,000 to < 70,000*

[6] *70,000 to < 80,000*

[7] *100,000 to < 200,000*
[8] *200,000 to < 300,000*
[9] *300,000 to < 400,000*
[10] *400,000 to < 500,000*
[11] *700,000 to < 800,000*
[12] *900,000 to < 1,000,000*
[13] *1,000,000 to < 2,000,000*
[14] *$200 million to < $300 million*
[15] *$600 million to < $700 million*

4.16 In terms of the inputs altered, the resubmission stated that the 29%, which was based on an IQVIA report of patients receiving PBS listed treatment in 2022 (N=905,487), used to inform the proportion of episodic migraine patients who received pharmacological treatment was likely underestimated. The resubmission stated that the IQVIA data analysed patients who received PBS treatments during August 2022 only and likely did not capture the episodic nature of acute migraine attacks. Additionally, it did not include over-the-counter medications. The resubmission did note that the IQVIA data did provide data on the type of treatment received, and that of the 29% of patients who received a PBS-listed migraine treatment in August 2022, 56.3% of patients received acute migraine treatments (rather than preventative treatments) and that this value aligned with other published data sourced by the resubmission; see Table 6.

Table 6: Comparison of proportions of episodic migraine patients receiving pharmacological treatments

	Source	Study size	% of episodic migraine patients treated with pharmacological treatments	Combined average
July 2023 base case – IQVIA PBS analysis, August 2022	PBS statistics	905,487	29%	-
March 2024 base case – IQVIA PBS analysis, August 2022	PBS statistics	905,487	56.3%[a]	56.6%
Stark (2007)	Australian GP survey	5,663	79.3%	
Gendolla (2022)	German statuary health insurance data	120,170	55.4%	
Lipton (2019)	USA longitudinal, internet-based survey	13,624	35.5%	

Source: Table 9, p18 of the early re-entry resubmission
GP = general practice; PBS = Pharmaceutical Benefits Scheme; USA = United States of America
[a] 56.3% of the 29% of patients who received PBS treatments in August 2022 received acute migraine treatments

4.17 The resubmission stated that the proportion of patients who failed at least 2 triptans derived from the BHV3000-301-302-303 studies of 9.3% was likely an underestimation. Therefore, the resubmission conducted a desktop literature review of studies that specifically reported the proportion of non-responders to ≥ 2 triptans; see Table 7. The resubmission stated that the use of the combined average (12.4%) in the revised utilisation estimates was conservative as it did not account for the additional proportion of migraine patients contraindicated to triptans (average 12.8%) or for those who have discontinued triptans due to adverse events (average 19.7%) and that the total estimate of migraine patients who are contraindicated to triptans or have had to discontinue triptans due to adverse events may be between 30 to 40%.

Table 7: Comparison of proportions of migraine patients who have failed at least 2 triptans

	Source	Study size	% of migraine patients who have failed ≥ 2 triptans	Combined average
July 2023 base case – pooled data from the BHV3000-301-302-303 trials	Clinical trials	3,507	9.3%	12.4%
Gendolla (2022)	German statuary health insurance data	120,170	13.1%	
Lipton (2020)	USA Optum Clinformatics health claims data	162,322	9.3%	
Lombard (2020)	European Adlephi Migraine Disease Specific Programme - Cross sectional survey	1,413	19.5%	
Ruscheweyh (2023)	German Migraine and Headache Society Headache Registry	2,284	13.1%	

Source: Table 10, p19 of the early re-entry resubmission
PBS = Pharmaceutical Benefits Scheme; USA = United States of America

4.18 The resubmission stated that the higher uptake rates applied in the revised utilisation estimates captured the uncertainty regarding the proportion of patients who had failed at least 2 triptans and the high disease burden in this patient population.

4.19 Table 8 presents the revised utilisation and financial impact estimates and provides a comparison with the July 2023 results.

Table 8: Estimated utilisation and financial impact estimates*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients continuing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS less co-payments[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2023 submission						
Estimated extent of use						
Number of patients initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients continuing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients treated[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS less co-payments*	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 8, p17 of the early re-entry resubmission, Excel workbook – Rimegepant_Acute_Migraine_UCM_FINAL_22DEC2023.xlsx and Table 16, p37 of the rimegepant PSD, July 2023
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Assuming 2.35 scripts of the 2 tablet pack per patient in 1 month initiation period and 6.46 scripts of the 8 tablet pack per patient for the remaining 11 months and then 7.05 scripts of the 8 tablet pack per patient per year 12-month thereafter
[b] Calculated during evaluation using General ordinary: $30.00, General safety net: $7.30, Concessional ordinary: $7.30, RPBS ordinary $7.30.
* The number of patients receiving the one month initiation (of 2.35 scripts) was corrected to equal the number of patients initiating treatment and the number of patients receiving the 11 months continuing treatment (6.46 scripts) was corrected to equal the number of continuing patients. Co-payments were also updated (PBS co-payment was increased from $21.47 to $22.70 and RPBS co-payment was increased from $4.76 to $4.79).
The redacted values correspond to the following ranges:
[1] *40,000 to < 50,000*
[2] *60,000 to < 70,000*
[3] *50,000 to < 60,000*
[4] *20,000 to < 30,000*
[5] *90,000 to < 100,000*
[6] *100,000 to < 200,000*
[7] *70,000 to < 80,000*
[8] *200,000 to < 300,000*
[9] *400,000 to < 500,000*
[10] *700,000 to < 800,000*
[11] *900,000 to < 1,000,000*
[12] *1,000,000 to < 2,000,000*
[13] *$30 million to < $40 million*
[14] *$60 million to < $70 million*
[15] *$100 million to < $200 million*
[16] *10,000 to < 20,000*
[17] *5,000 to < 10,000*
[18] *30,000 to < 40,000*
[19] *300,000 to < 400,000*
[20] *$0 to < $10 million*
[21] *$20 million to < $30 million*
[22] *$40 million to < $50 million*
[23] *$70 million to < $80 million*

4.20 The revised estimated net cost to the PBS/RPBS was $30 million to < $40 million in Year 1, increasing to $100 million to < $200 million in Year 6 and totalling an estimated $600 million to < $700 million over the first 6 years of listing. The July 2023 submission estimated a total cost of $200 million to < $300 million over the first 6 years of listing (using the price proposed in the July 2023 submission).

Financial management – Risk Sharing Arrangements

4.21 In July 2023, the PBAC advised that an RSA would be required to manage the uncertainties in rimegepant eligibility, uptake and use (paragraph 7.12, rimegepant PSD, July 2023).

4.22 The resubmission stated that a level of uncertainty in the parameters informing the financial estimates remained, particularly in the proportion of patients who had failed at least two triptans.

4.23 The resubmission proposed a three-tiered RSA in which a rebate of [redacted]% would apply for expenditure between Tier 1, the estimated PBS/RPBS expenditure, and Tier 2, which was approximately [redacted]% higher. A rebate of [redacted]% would apply to expenditure between Tier 2 and Tier 3, which was approximately [redacted]% higher than Tier 2 and [redacted]% higher than Tier 1, and a [redacted]% rebate would apply for use above Tier 3; see Table 9.

4.24 The Secretariat noted that the structure of the proposed RSA was not appropriate and does not manage the identified risks. The Secretariat noted that usually, as use beyond the financial estimates may reflect use in a less cost-effective cohort, an RSA would ensure that this additional, potentially not cost-effective utilisation is discounted to a certain extent; however, in the proposed RSA, the financial uncertainty for Government is increased, as the Commonwealth pays more as use further exceeds the estimated level. If there is concern that the patient population is uncertain, then the Secretariat advised that there should be a single cap with a rebate of 100% applying at the level of the financial estimates.

Table 9: Proposed RSA expenditure caps*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Tier 1: estimated PBS/RPBS expenditure	$[redacted] [1]	$[redacted] [2]	$[redacted] [3]	$[redacted] [3]	$[redacted] [3]	$[redacted] [3]
Rebate to Tier 2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Tier 2	$[redacted] [4]	$[redacted] [5]	$[redacted] [3]	$[redacted] [3]	$[redacted] [6]	$[redacted] [6]
Rebate to Tier 3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Tier 3	$[redacted] [7]	$[redacted] [8]	$[redacted] [3]	$[redacted] [3]	$[redacted] [6]	$[redacted] [6]
Rebate beyond Tier 3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Source: Table 11, p18 of the early re-entry resubmission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RSA = risk-sharing arrangement

* Proposed expenditure caps have not been revised to align with the corrected financial expenditure

The redacted values correspond to the following ranges:

[1] *$20 million to < $30 million*

[2] *$60 million to < $70 million*

[3] *$100 million to < $200 million*

[4] *$30 million to < $40 million*

[5] *$70 million to < $80 million*

[6] *$200 million to < $300 million*

[7] *$40 million to < $50 million*

[8] *$80 million to < $90 million*

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC did not recommend rimegepant for the acute treatment of migraine in adults who have not responded adequately, are intolerant or contraindicated to analgesics and at least two selective 5-hydroxytryptamine receptor agonists (triptans). The PBAC acknowledged that there was a clinical need for new, oral treatments for the acute treatment of migraine and considered that rimegepant provided a benefit over best supportive care (BSC) in terms of efficacy. However, the PBAC considered that the resubmission did not appropriately address the issues raised in July 2023 relating to the economic evaluation and the financial impact estimates. The PBAC noted that a number of the suggested changes from July 2023 were not incorporated into the revised economic model and that the revised model was highly optimistic. Despite this, the PBAC considered that the revised incremental cost-effectiveness ratio (ICER) presented in the resubmission was high and that rimegepant was not cost-effective at the price proposed. Further, the PBAC noted that although it had considered that the utilisation estimates presented in the July 2023 submission were

reasonable, the resubmission presented revised utilisation estimates in which the utilisation of rimegepant was increased by more than 3.5 times over the first 6 years listing. This resulted in an estimated financial impact that, despite the % reduction in price, was over 2.5 times higher than in July 2023. The PBAC noted that the patient population was difficult to define and considered that there would likely be broad use of rimegepant. However, the PBAC considered that the proposed risk sharing arrangement (RSA) was not reasonable and did not mitigate the significant financial risk to Government.

5.2 The PBAC acknowledged the consumer comments that supported the resubmission and highlighted the clinical need for effective migraine treatments.

5.3 The PBAC recalled that in July 2023 it had considered that:

- A single dose of rimegepant was superior compared to BSC in terms of treating acute migraine;
- The long-term treatment effect of rimegepant was uncertain, due to a lack of longer-term efficacy data; and
- Rimegepant was non-inferior compared to BSC in terms of safety.

5.4 The PBAC recalled that it had specified the following revisions to the economic model would be required to achieve an acceptable ICER (see Table 1 and paragraph 4.9 for further details):

i. Efficacy inputs should be based on data from the modified intention-to-treat (mITT) analysis, as the use of the *post hoc*, pooled subgroup analysis was not adequately justified;

ii. The time horizon should be reduced from 5 years to 1 year, given the assumption the efficacy of rimegepant would be maintained was uncertain as the trial results related to a single migraine attack;

iii. The baseline utility should be based on the Migraine Specific Quality of Life (MSQ) questionnaire data and then the utilities from Stafford et al (2012) should be adjusted using the multiplicative approach;

iv. Patients who discontinued treatment with rimegepant should transition to the placebo/BSC non-responder arm, rather than the placebo/BSC responder arm; and

v. Noting that these changes resulted in an ICER of $45,000 to < $55,000 per QALY, the PBAC requested a price reduction so that the resultant ICER was equivalent to that presented in the July 2023 submission, i.e., $15,000 to < $25,000 per quality adjusted life year (QALY) gained, and which resulted in a price per tablet at the DPMQ level of approximately $ to $.

5.5 The PBAC noted that the resubmission accepted two of the suggested changes (as requested in (iii) and (iv) above), reduced the time horizon to 3 years and proposed an approximate % price reduction; and that these changes resulted in an ICER of

$25,000 to < $35,000 per QALY gained. The PBAC considered the economic model presented in the resubmission included optimistic assumptions regarding the incremental benefit of rimegepant (i.e., the model was based on the *post hoc*, pooled subgroup analysis of the secondary outcome of pain relief at 2 hours post dose which reported an additional 33% of rimegepant patients achieved pain relief at 2 hours compared to placebo as compared to an additional 14% if the mITT population was used) and further noted the ICER was substantially higher than what the PBAC previously considered would be cost effective ($15,000 to < $25,000 as requested in (v) above). The PBAC noted applying the efficacy inputs from the mITT population (as requested in (i) above; in which an additional 14% of rimegepant patients achieved pain relief at 2 hours) and reducing the time horizon to 1 year (as requested in (ii) above) increased the ICER to $35,000 to < $45,000 per QALY gained. The PBAC considered the ICER was high and uncertain and that rimegepant was not cost-effective at the price proposed in the resubmission.

5.6 The PBAC recalled that it had advised that revised financial estimates be presented which were based on the utilisation estimates provided by the sponsor in the July 2023 submission and which incorporated the revised price. The PBAC noted the eligible rimegepant population was expanded considerably in the resubmission, with the proportion of patients with episodic migraine who received a pharmacological treatment increased from 29% to 56.6%, the proportion of patients with episodic migraine who failed at least 2 triptans increased from 9.3% to 12.4% and the uptake rates increased from [redacted]% in Year 1 and [redacted]% in Year 6 to [redacted]% and [redacted]% respectively. The PBAC noted the utilisation of rimegepant was increased by more than 3.5 times over the first 6 years of listing, compared to the July 2023 submission. The PBAC, noting that the resultant financial impact estimates ($600 million to < $700 million over the first 6 years) were increased by more than 2.5 times compared to those presented in the July 2023 submission, considered that the cost to the PBS/RPBS was very high. Further, the PBAC noted that the resubmission considered that the revised utilisation was likely underestimated as the proportion of patients who had failed at least 2 triptans (12.4%) was highly uncertain and likely higher in practice.

5.7 The PBAC noted the resubmission proposed a three-tiered RSA, with expenditure caps for Tiers 2 and 3 higher than the estimated PBS expenditure and rebates decreasing as expenditure increased (as described in paragraph 4.23). Noting (i) the high proposed cost to the PBS/RPBS, (ii) the uncertainty in the size of the proposed eligible population, (iii) the high risk of use in patients who have not failed at least 2 triptans and in the chronic migraine population, and (iv) the high risk of continuing use in patients who do not have an adequate response to rimegepant, the PBAC considered that the proposed RSA did not adequately manage the risk to Government. Noting that the size of the eligible patient population was highly uncertain and that it was difficult to define the appropriate use of rimegepant, the PBAC advised that any future RSA should consist of a single expenditure cap, beyond which a rebate of 100% is applied.

5.8 In terms of the restriction, the PBAC noted that the requested changes were made and considered that the proposed restriction was reasonable.

5.9 The PBAC considered a resubmission for rimegepant should address the issues raised above and in the July 2023 PBAC PSD. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

5.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

6 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.

7 Sponsor's Comment

While disappointed with the PBAC's decision not to recommend rimegepant for the treatment of acute migraine attacks, Pfizer welcomes the PBAC's continued acknowledgment of the burden of acute migraine and the clinical unmet need for novel effective treatments such as rimegepant.

Pfizer's resubmission included significant changes intended to address the early re-entry criteria. Pfizer hopes to continue working with the PBAC and the Department of Health and Aged Care to enable access for rimegepant to patients suffering from acute migraine attacks. Pfizer views the PBAC preferred financial estimates as likely underestimating the potential use in clinical practice substantially, for use of rimegepant in acute migraine attacks within the Pfizer proposed restrictions.