

7.16 OBINUTUZUMAB, Solution for I.V. infusion, 1000 mg in 40 mL, GAZYVA®, Roche Pty Ltd

1 Purpose of Application

1.1 The minor resubmission requested Section 100 Efficient Funding of Chemotherapy listing for obinutuzumab for:

- previously untreated advanced follicular lymphoma (Stage II bulky or Stage III/IV); and
- rituximab-refractory follicular lymphoma.

2 Requested listing

2.1 The resubmission requested the following combined restriction for previously untreated and rituximab-refractory follicular lymphoma. Separate listings were proposed for the induction setting, the maintenance setting and for grandfathered patients.

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

Induction setting – previously untreated

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	9	Published Public: \$5,376.83 Private: \$5,489.57 Effective Public: \$ Private: \$	GAZYVA® Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Previously untreated or rituximab refractory
Severity:	<i>Stage II bulky or Stage III/IV</i>
Condition:	CD20 positive follicular lymphoma
PBS Indication:	Previously untreated Stage II bulky or Stage III/IV CD20 positive follicular lymphoma or Rituximab refractory follicular lymphoma
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined <input checked="" type="checkbox"/> Authority Required - Telephone

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Treatment phase:	Induction treatment or Re-induction treatment
Treatment criteria:	<p>The condition must be symptomatic, AND The condition must be previously untreated, OR The condition must be for rituximab-refractory purposes only refractory to treatment with rituximab for this condition AND The treatment must be in combination with PBS-subsidised chemotherapy, AND The treatment must be for induction treatment purposes only, OR The treatment must be for re-induction treatment purposes only AND Patient must not receive more than the number of cycles of treatment recommended by standard guidelines for the partner chemotherapy under this restriction.</p>
Prescriber Instructions	<p>A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition. <i>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition</i></p> <p>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</p> <p>A patient may only qualify for PBS-subsidised induction treatment once in a lifetime under either this restriction <u>or</u> the rituximab-refractory re-induction restriction.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. <i>No increase in the maximum quantity or number of units may be authorised.</i> Special Pricing Arrangements apply.</p>

Rituximab-refractory re-induction setting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	9-7	<p><u>Published</u> Public: \$5,376.83 Private: \$5,489.57 <u>Effective</u> Public: \$ [REDACTED] Private: \$ [REDACTED]</p>	GAZYVA® Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Previously untreated or rituximab-refractory
Severity:	Stage II bulky or Stage III/IV
Condition:	CD20 positive follicular lymphoma
PBS Indication:	Previously untreated Stage II bulky or Stage III/IV CD20 positive follicular lymphoma or Rituximab-refractory follicular lymphoma

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Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined <input checked="" type="checkbox"/> Authority Required - Telephone
Treatment phase:	Induction treatment or Re-induction treatment
Treatment criteria:	<p>The condition must be symptomatic, AND The condition must be previously untreated, OR The condition must be for rituximab-refractory purposes only-refractory to treatment with rituximab for this condition AND The treatment must be in combination with PBS-subsidised chemotherapy bendamustine, AND The treatment must be for induction treatment purposes only, OR The treatment must be for re-induction treatment purposes only AND Patient must not receive more than the number of cycles of treatment recommended by standard guidelines for the partner chemotherapy under this restriction.</p>
Prescriber Instructions	<p>A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition. Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition</p> <p>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</p> <p>A patient may only qualify for PBS-subsidised induction treatment once in a lifetime under either this restriction or the previously untreated induction restriction.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.</p>

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Maintenance therapy - previously untreated setting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Manufacturer	Name and
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	5	<u>Published</u> Public: \$5,376.83 Private: \$5,489.57 <u>Effective</u> Public: \$ [REDACTED] Private: \$ [REDACTED]	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Previously untreated or rituximab refractory
Severity:	<i>Stage II bulky or Stage III/IV</i>
Condition:	CD20 positive follicular lymphoma
PBS Indication:	Stage II bulky or Stage III/IV CD20 positive follicular lymphoma or Rituximab refractory follicular lymphoma
Treatment phase:	Maintenance therapy
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined <input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	The treatment must be as monotherapy, AND The treatment must be maintenance therapy, AND Patient must have demonstrated a partial or complete response to the PBS-subsidised obinutuzumab and chemotherapy induction treatment, OR Patient must have demonstrated a partial or complete response, or stable disease to the PBS-subsidised obinutuzumab and chemotherapy re-induction treatment AND Patient must not receive more than 12 doses or 2 years duration of treatment, whichever comes first, under this restriction.
Prescriber Instructions	A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition. <i>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition</i> A patient may only qualify for PBS-subsidised maintenance treatment once in a lifetime under <i>either</i> this restriction or <i>the rituximab-refractory maintenance restriction</i> .
Administrative Advice	No increase in the maximum number of repeats may be authorised. <i>No increase in the maximum quantity or number of units may be authorised.</i> Special Pricing Arrangements apply.

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Maintenance therapy – rituximab-refractory setting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Manufacturer	Name and
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	5	<u>Published</u> Public: \$5,376.83 Private: \$5,489.57 <u>Effective</u> Public: \$ [REDACTED] Private: \$ [REDACTED]	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Severity:	<i>Stage II bulky or Stage III/IV</i>
Condition:	CD20 positive follicular lymphoma
PBS Indication:	Rituximab-refractory follicular lymphoma
Treatment phase:	Maintenance therapy
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	The treatment must be as monotherapy, AND The treatment must be maintenance therapy, AND Patient must have demonstrated a partial or complete response, or stable disease to the PBS-subsidised obinutuzumab and chemotherapy bendamustine re-induction treatment AND Patient must not receive more than 12 doses or 2 years duration of treatment, whichever comes first, under this restriction.
Prescriber Instructions	<i>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition A patient may only qualify for PBS-subsidised maintenance treatment once in a lifetime under either this restriction or the previously untreated maintenance restriction.</i>
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

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Grandfathering restriction

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	8	<u>Published</u> Public: \$5,376.83 Private: \$5,489.57 <u>Effective</u> Public: \$ [REDACTED] Private: \$ [REDACTED]	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Previously untreated or rituximab refractory
Severity:	<i>Stage II bulky or Stage III/IV</i>
Condition:	CD20 positive follicular lymphoma
PBS Indication:	Previously untreated Stage II bulky or Stage III/IV CD20 positive follicular lymphoma or Rituximab-refractory follicular lymphoma
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined <input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	<p>Patient must have received treatment with obinutuzumab for this condition prior to the [PBS listing date], AND ONE OF THE FOLLOWING MUST APPLY:</p> <p>(i) The treatment must be in combination with PBS-subsidised chemotherapy AND The treatment must be for induction treatment purposes only</p> <p>OR</p> <p>(ii) The treatment must be for re-induction treatment purposes only, AND <i>The condition must be refractory to treatment with rituximab for this condition</i> AND <i>The treatment must be in combination with PBS-subsidised bendamustine</i></p> <p>OR</p> <p>(iii) <i>The treatment must be maintenance therapy, AND</i> <i>Patient must have demonstrated a partial or complete response to either the PBS-subsidised chemotherapy induction treatment or obinutuzumab and bendamustine re-induction treatment,</i> AND <i>The treatment must be as monotherapy,</i> AND <i>Patient must not receive more than 11 doses or 2 years duration of treatment, whichever comes first, under this restriction.</i></p> <p>AND Patient must not receive more than the number of cycles of treatment recommended by standard guidelines for the partner chemotherapy under this restriction.</p>

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Prescriber Instructions	<p>A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition.</p> <p><i>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition</i></p> <p>A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.</p> <p><i>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</i></p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p>Special Pricing Arrangements apply.</p>

2.3 The resubmission proposed a special pricing arrangement with a published dispensed price for maximum amount (DMPA) of \$5,376.22 and an effective DPMA of \$ [REDACTED] (public hospital setting). Compared with the previous submission for previously untreated advanced follicular lymphoma, this represented a [REDACTED]% reduction to the effective price (the previous submission proposed an effective DPMA of \$ [REDACTED]).

Combined restriction for the two settings

2.4 The resubmission combined the restrictions for induction and re-induction therapy (i.e. in the previously untreated and rituximab-refractory settings, respectively). The PBAC considered this was not appropriate and that separate restrictions would be required given the maximum number of repeats differs between the two settings. The PBAC considered this would reduce wastage in the re-induction setting (i.e. rituximab-refractory disease) where fewer repeats are required. The doses are:

- for induction of previously untreated follicular lymphoma, a maximum of nine repeats would be required, as proposed. Study sites in the pivotal trial (GALLIUM) chose one of three chemotherapy-backbone regimens: cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP); cyclophosphamide, vincristine and prednisone (CVP); or bendamustine. These regimens use six to eight treatment cycles and thus require eight to ten doses of obinutuzumab. (Per the GALLIUM trial, obinutuzumab 1,000 mg is administered on Days 1, 8 and 15 of the first treatment cycle, then on Day 1 of each subsequent cycle); while
- for re-induction in rituximab-refractory disease, a maximum of seven repeats would be required (rather than the proposed nine repeats). The re-induction regimen in this setting is obinutuzumab + bendamustine, which is used for up to six treatment cycles, thus requiring a maximum of eight doses of obinutuzumab. (Per the GADOLIN trial, obinutuzumab 1000 mg is administered on Days 1, 8 and 15 of the first treatment cycle, then on Day 1 of each subsequent cycle).

- 2.5 As outlined above, bendamustine is the only chemotherapy backbone that was used with obinutuzumab in the clinical trial in the rituximab-refractory setting (GADOLIN). The proposed clinical criteria in the previous submission had included “The treatment must be in combination with bendamustine”, whereas the combined restriction replaces this with “The treatment must be in combination with PBS-subsidised chemotherapy”.
- 2.6 Separate initiating and continuing restrictions may also be required. The continuing restriction should state ‘Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition’ along with ‘Patient must have previously received PBS-subsidised treatment with this drug for this condition’.

Once per lifetime requirement

- 2.7 The resubmission proposed that obinutuzumab would only be PBS-subsidised once per lifetime. The PBAC noted that the once per lifetime requirement cannot be administered by the Department of Human Services in an Authority Required (Streamlined) listing. That is, it would be up to the prescriber to comply with the once per lifetime requirement under the proposed streamlined listing.
- 2.8 The PBAC considered that there was a substantial risk of re-use of obinutuzumab following relapse if it had been used in first-line, and thus considered that the once per lifetime requirement should be administered by the Department of Human Services. The PBAC therefore considered that an Authority Required – Telephone restriction would be appropriate.

Flow-on changes to bendamustine

- 2.9 A number of flow-on changes would be required to the bendamustine restriction to facilitate PBS-subsidised combination therapy. The current bendamustine PBS-listing is for induction therapy in previously untreated stage III or IV indolent CD20 positive non-Hodgkin’s lymphoma, and the treatment must be in combination with rituximab.
- 2.10 Thus, the PBAC considered that the following changes would be required in previously untreated follicular lymphoma:
- the bendamustine induction restriction states that “Treatment must be in combination with rituximab”. Obinutuzumab would also need to be referenced to facilitate obinutuzumab + bendamustine combination therapy, noting that in the pivotal trial (GALLIUM), 57% of patients received obinutuzumab + bendamustine as the induction regimen. The bendamustine restriction could therefore become “Treatment must be in combination with either rituximab or obinutuzumab”.
 - the proposed obinutuzumab restriction includes stage II bulky CD20 positive follicular lymphoma. The PBAC considered that the bendamustine restriction

should be amended to allow use in stage II bulky CD20 positive follicular lymphoma as well as in Stage III or IV follicular lymphoma when used in combination with either rituximab or obinutuzumab.

- 2.11 In rituximab-refractory follicular lymphoma, the PBAC noted that bendamustine is not currently PBS-subsidised, so a new listing would be required for bendamustine in this setting. The PBAC recalled that in March 2015 it had considered a submission for bendamustine monotherapy in rituximab-refractory indolent Non-Hodgkin's Lymphoma (iNHL) (as part of a submission that also sought listing for previously untreated indolent NHL and Mantle Cell Lymphoma). The PBAC recalled that it had not recommended bendamustine monotherapy in rituximab-refractory iNHL noting the lack of comparative information, and that it was not possible to draw any conclusions regarding the comparative effectiveness, safety and cost-effectiveness of bendamustine in this setting. (Paragraph 7.13, Bendamustine Public Summary Document, March 2015).
- 2.12 The PBAC noted that the only evidence presented for bendamustine combination therapy in this setting (rituximab-refractory follicular lymphoma) was the GADOLIN trial (obinutuzumab + bendamustine versus bendamustine monotherapy).

Other matters relating to the restriction

- 2.13 The November 2017 submission stated that ■■■ patients are likely to receive obinutuzumab initial treatment under a patient access program. The resubmission proposed a grandfather restriction for the induction and re-induction settings. It was assumed that patients must have received at least one prior dose of obinutuzumab to be eligible for grandfathering therapy with 8 repeats proposed. As outlined previously, fewer repeats would be required for use as re-induction in rituximab-refractory disease.
- 2.14 The resubmission did not propose a grandfather restriction for the maintenance setting, which indicated that the resubmission assumed that all patients who require grandfathered access would be in the induction setting at the time of PBS-listing.
- 2.15 The PBAC considered that the restriction should specify that "No increase in the maximum quantity or number of units may be authorised" under the Administrative Advice.

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

3 Background

- 3.1 Obinutuzumab was previously considered by the PBAC:
- In November 2017 for previously untreated advanced follicular lymphoma. The intervention in this setting is obinutuzumab + chemotherapy (CHOP, CVP or bendamustine) as induction treatment followed by obinutuzumab maintenance

monotherapy. The comparator was rituximab + chemotherapy for induction treatment and rituximab monotherapy for maintenance treatment.

- In November 2016 for rituximab-refractory follicular lymphoma. In this setting, obinutuzumab is proposed for use in combination with bendamustine as re-induction treatment followed by obinutuzumab maintenance monotherapy. The comparator was best supportive care.

3.2 The comparators were unchanged from the previous submissions, and were previously accepted by the PBAC.

Key changes versus the previous submissions

3.3 Rather than specifically addressing each of the PBAC's previous concerns, the resubmission proposed a price for obinutuzumab that aimed to [REDACTED]

[REDACTED] The resubmission noted that the price would need to account for the additional treatment costs associated with obinutuzumab maintenance following obinutuzumab + bendamustine induction, given that rituximab maintenance following rituximab + bendamustine induction is not PBS reimbursed.

3.4 The resubmission also proposed [REDACTED], and a combined restriction for both indications. As patients would only qualify for obinutuzumab once per lifetime, the resubmission considered that clinical judgement could be used to determine which setting would optimise the benefit for an individual patient. This may help address the PBAC's previous concerns that "given the prognosis of the disease and its high response to rituximab, the clinical need for obinutuzumab in the first-line setting may be limited to those patients able to tolerate its increased toxicity, and who do not optimally respond to rituximab-based regimes (eg. with a short time to progression). The PBAC considered that while this small sub-group of patients could benefit from obinutuzumab over rituximab, the submission did not identify such a sub-group" (Paragraph 7.3, obinutuzumab PSD, November 2017).

3.5 The key changes are outlined in the table below.

Table 1: Changes made versus the previous submissions

	Previous submissions		Current resubmission: follicular lymphoma
	Nov 2016: Rituximab-refractory	Nov 2017: Previously untreated	
Context			
Requested price	DPMA (effective price) Public: \$ █████ SPA Private: \$ █████ SPA	DPMA (effective price) Public: \$ █████ SPA Private: \$ █████ SPA	DPMA (effective price) Public: \$ █████ SPA Private: \$ █████ SPA
Place in therapy	Rituximab-refractory FL	Previously untreated FL PBAC considered the clinical need in 1st-line may be restricted to a subgroup of patients only, that had not been identified in the submission” (Para 7.3).	Consolidated restriction for use once per lifetime in either: previously untreated FL; or rituximab-refractory FL
Economic evaluation			
ICER	\$ █████/QALY. PBAC considered this was “highly uncertain and was likely to be significantly underestimated” (Para 7.7).	\$ █████/QALY. PBAC considered this was highly uncertain, as the economic model assumed an advantage in survival based on delayed disease progression that is unable to be fully tested due to immature OS data (Para 7.1).	<u>Versus previously untreated:</u> █████ Only changes were reduced obinutuzumab price plus updated rituximab price (to the 1 Feb 2018 price). All other parameters unchanged.
Utilisation and costs			
Cost to PBS/RPBS	More than \$100 million over 6 years.	\$60-\$100 million over 6 years. Based on 100% of eligible pts receiving maintenance tx in each arm.	<u>Versus previously untreated:</u> Save of less than \$10 million over 6 years. Changes were: updated drug prices; and assumed a █████% difference in maintenance use.

Source: Table 1.1 p 4 of the resubmission, ‘Net cost of drug to Government’ worksheet, ‘Financial cost to PBS.xlsx from November 2016, Obinutuzumab PBAC Minutes, November 2016, Obinutuzumab PBAC Minutes, November 2017.

DPMA = dispensed price for maximum amount; FL = follicular lymphoma; ICER = incremental cost-effectiveness ratio; SPA = special pricing arrangement; QALY = quality adjusted life-year

3.6 For the previously untreated advanced follicular lymphoma indication, outstanding matters of concern that were not specifically addressed by the resubmission included:

- the clinical benefits over rituximab were uncertain, with no demonstrated improvement in quality of life or overall survival (OS) and an inferior comparative safety profile;
- the OS data from the GALLIUM trial were immature, with less than █████% of patients in each arm having died as of the September 2016 data cut;
- among the various chemotherapy regimens used in the GALLIUM trial, treatment with obinutuzumab + bendamustine was associated with higher rates of grade 3 to 5 infection and second neoplasm during the maintenance and follow-up phases. The PBAC noted uncertainty regarding the clinical place of obinutuzumab

- + bendamustine combination followed by obinutuzumab maintenance in this population; and
 - the incidence of serious adverse events was █████% higher in patients ≥ 65 years treated with obinutuzumab + chemotherapy versus those treated with rituximab + chemotherapy in the GALLIUM trial, and that there were also more AEs leading to treatment discontinuation and AEs leading to death in this elderly population (Paragraphs 7.1, 7.2, 7.7 and 7.8, obinutuzumab PSD, November 2017).
- 3.7 For rituximab-refractory follicular lymphoma, outstanding matters of concern that were not specifically addressed by the resubmission included:
- the magnitude of any OS gain was highly uncertain due to the immaturity of the trial data presented in the submission;
 - the PBAC accepted best supportive care as the appropriate comparator, and considered that bendamustine efficacy was a reasonable proxy. However, as bendamustine was considered not cost-effective for the treatment of rituximab-refractory iNHL at the March 2015 PBAC meeting (refer to Paragraph 2.10, above) and is not PBS-subsidised for this patient population, the PBAC considered that the cost of bendamustine could not be used as a proxy for the cost of best supportive care;
 - obinutuzumab plus bendamustine followed by obinutuzumab maintenance was of inferior safety compared with bendamustine monotherapy (associated with increased rates of infusion-related reactions and musculoskeletal and cardiac events); and
 - the incremental cost-effectiveness ratio (ICER) was highly uncertain and was likely to be significantly underestimated due to several issues with the economic model. These included the extrapolation of immature trial data, the use of an inappropriate time horizon and inappropriate costs in the comparator arm (Paragraphs 7.3, 7.5 and 7.7, obinutuzumab PSD, November 2016).

TGA registration

- 3.8 The November 2017 submission for previously untreated advanced follicular lymphoma was made under the TGA-PBAC parallel process. Since then, obinutuzumab has been TGA registered for the following indication:

“obinutuzumab in combination with chemotherapy followed by obinutuzumab maintenance is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.”

- 3.9 Obinutuzumab is also TGA-registered for use in combination with bendamustine, followed by obinutuzumab maintenance, for patients with follicular lymphoma who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

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 as it was a minor resubmission.

Consumer comments

4.1 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the fear of relapse as a significant mental and physiological challenge. Lymphoma Australia outlined the importance of having a range of therapeutic options given that patients often experience multiple relapses.

Economic analysis

4.2 The resubmission made the following changes to the economic evaluation for previously untreated advanced follicular lymphoma:

- the price of obinutuzumab was reduced from an approved ex-manufacturer price (AEMP) of \$ [REDACTED] to \$ [REDACTED] (a [REDACTED] % reduction);
- the price of rituximab was reduced by [REDACTED] % to reflect the price on 1 February 2018 (reduced to broaden the PBS listing to CD20 positive lymphoid cancers); and
- dispensing fees and mark-ups were updated to reflect 1 December 2017 values.

4.3 The results of the stepped economic evaluation are presented in Table 2. As a minor resubmission, the changes were not evaluated.

Table 2: Results of the stepped economic evaluation

Step and component	Obinutuzumab regimen	Rituximab regimen	Increment
Step 1: trial-based costs and outcomes (60.1 and 58.4 months of data)			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 2: modelled evaluation across 20 years			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 3: incorporation of medical resource use costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 4: incorporation of adverse event costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 5: Inclusion of post-progression therapy			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 6: Inclusion of end of life costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Step 7: Convergence of survival curves			
Costs	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			[REDACTED]
Results from previous submission			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	8.42	7.69	0.73
Incremental cost/QALY			\$ [REDACTED]

Source: Table 2.2, p 10 of the resubmission; Updated Economic Evaluation.xlsx, worksheet 'Results Table'

Note: Steps were updated compared with those presented in the resubmission to remove redundant steps. Further, the resubmission updated the steps to reflect the previous ESC advice (from October 2017) that the effective AEMP should be applied from Step 1 onwards (rather than the published price).

QALY = quality adjusted life-year

4.4 In the model presented, obinutuzumab was [REDACTED] compared with an ICER of [REDACTED]

\$15,000 -\$45,000 per quality adjusted life-year (QALY) in the previous submission. The change was due to the lower proposed price of obinutuzumab.

- 4.5 In November 2017, the PBAC had considered that the cost-effectiveness against rituximab was highly uncertain, as the economic model assumed an advantage in survival based on delayed disease progression that was unable to be fully tested due to immature OS data (Paragraph 7.1, obinutuzumab PSD, November 2017).
- 4.6 Total costs were \$ [redacted] lower in the obinutuzumab arm than the comparator arm. The breakdown of costs is presented in the table below. Note that costs associated with the chemotherapy backbone used during induction were not included in the economic model. This assumed the chemotherapy backbone used during induction treatment would not change with the PBS listing of obinutuzumab.

Table 3: Breakdown of costs in the resubmission’s revised economic evaluation

Cost	Obinutuzumab	Rituximab	Increment
First line			
Cost of antibody ^a			
- Induction	\$ [redacted]	\$ [redacted]	[redacted]
- Maintenance	\$ [redacted]	\$ [redacted]	[redacted]
- Total	\$ [redacted]	\$ [redacted]	[redacted]
Administration costs	\$ [redacted]	\$ [redacted]	[redacted]
Cost of adverse events	\$ [redacted]	\$ [redacted]	[redacted]
Medical Resource Use cost	\$ [redacted]	\$ [redacted]	[redacted]
Difference in first-line	\$ [redacted]	\$ [redacted]	[redacted]
Subsequent line			
Cost of therapy	\$ [redacted]	\$ [redacted]	[redacted]
Medical Resource Use cost	\$ [redacted]	\$ [redacted]	[redacted]
End of life cost			
End of life cost	\$ [redacted]	\$ [redacted]	[redacted]
Mean total cost			
Total	\$ [redacted]	\$ [redacted]	[redacted]

Source: Updated Economic Evaluation.xlsx, worksheet 'Results Table'

^a Induction and maintenance costs were separated by setting to "0" cells F7 and L7 (or F8 and L8) in the 'Drug doses & acquisition costs' worksheet.

- 4.7 Obinutuzumab therapy (induction and maintenance) was associated with [redacted] costs of \$ [redacted] compared with rituximab in the first-line setting. However, the economic model assumed that 100% of eligible patients would receive maintenance therapy in each arm. This did not align with the proportions proposed in the financial estimates (which were [redacted]% of eligible patients in the obinutuzumab arm and [redacted]% in the rituximab arm, refer to 'Estimated PBS usage & financial implications' section). This was tested in sensitivity analyses conducted during preparation of the minor overview (Table 4).

4.8 The maintenance costs were [REDACTED] in the rituximab arm because the cost per dose was [REDACTED]: \$ [REDACTED] per rituximab dose of 689 mg (based on the average dose received in the GALLIUM trial, where the planned dose was 375mg/m²); versus \$ [REDACTED] per obinutuzumab dose of 1,000 mg.

Table 4: Results of univariate sensitivity analyses conducted during preparation of the minor overview

Sensitivity analyses	Δ cost	Δ QALY	ICER
Base case	[REDACTED]	0.730	[REDACTED]
% of pts receiving maintenance (base case: 100% in each arm)			
- 70% obinutuzumab; 61% rituximab	[REDACTED]	0.73	[REDACTED]
- 70% obinutuzumab; 55.8% rituximab	[REDACTED]	0.73	[REDACTED]
- 70% obinutuzumab; 50% rituximab ^a	[REDACTED]	0.73	[REDACTED]
First-line costs only (base case: subsequent tx + end of life costs Δ [REDACTED])			
- No difference in subsequent therapy and end of life costs ^b	[REDACTED]	0.73	[REDACTED]
Rituximab price (base case: Feb 2018 price)			
- Further [REDACTED]% price reduction ^c	[REDACTED]	0.73	[REDACTED]

Source: Based on Updated Economic Evaluation.xlsx. Ital = figures in italics were calculated during preparation of the minor overview
 ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life-year

^a The value for rituximab for this analysis (50%) was chosen so as to test the sensitivity of the model to this parameter (not based on data)

^b In the 'Results Table' worksheet, costs were set to \$0 in Rows 45, 47 and 50

^c In the 'Model inputs' worksheet, costs were reduced by a further 16% in cells E41 and E43.

Rituximab-refractory follicular lymphoma

4.9 During preparation of the minor overview, the updated drug cost for obinutuzumab was applied to the model submitted in November 2016 for rituximab-refractory follicular lymphoma. No other changes were made to the model; the results are presented in the table below. The PBAC noted this was an indicative analysis only.

Table 5: Results of the economic evaluation for rituximab-refractory follicular lymphoma with updated drug costs

Step and component	Obinutuzumab + bende	Best supportive care	Increment
With updated obinutuzumab drug costs (no other changes were made to the model) ^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			\$ [REDACTED]
Base case presented in November 2016 (previous drug prices)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	4.38	3.00	1.38
Incremental cost/QALY			\$ [REDACTED]

Source: Table 8, page 21 of the obinutuzumab PBAC Minutes, November 2016; "Economic Evaluation.xlsx" spreadsheet submitted in November 2016; Ital = figures in italics were calculated during preparation of the minor overview
 QALY = quality-adjusted life year;

^aThe only change to the economic model that was submitted for consideration at the November 2016 PBAC meeting, was that the 'Treatment costs' worksheet, cell K57 was changed from \$ [REDACTED] to \$ [REDACTED] (the weighted cost per administration from the resubmission's updated economic model) .

4.10 The PBAC noted that when the obinutuzumab drug costs were reduced from \$ [REDACTED] to \$ [REDACTED] (AEMP) in the November 2016 economic model for rituximab-refractory follicular lymphoma, the ICER reduced by over half (from \$45,000/QALY-\$75,000/QALY to \$15,000/QALY-\$45,000/QALY).

were eligible for maintenance would receive maintenance therapy (in both the obinutuzumab and rituximab arms). The resubmission revised this based on estimates sourced from: a clinician survey for rituximab; and an advisory board meeting for obinutuzumab. The revised estimates are presented in the table below. Other assumptions regarding maintenance use remained unchanged (see footnote below Table 6).

Table 6: Proportion of patients likely to receive maintenance following induction therapy ^a

% of eligible pts (i.e. with CR or PR) who receive maintenance:	Initial submission	Resubmission estimate	PBAC consideration
Proposed algorithm -with obinutuzumab	100%	█% ^b	~80%
Current algorithm - with rituximab	100%	█% ^c	61%
Difference	-	█%	~19%

Source: Table 3.2, p13 of the resubmission

CR = complete response; PR = partial response

^a Other assumptions regarding maintenance utilisation remained unchanged and were:

- the proportion of patients who would be eligible for maintenance was based on the complete and partial response rates in the respective arms of GALLIUM, which were █% for obinutuzumab and █% for rituximab;
- the obinutuzumab dose was assumed to be 1,000 mg (fixed dose) and the rituximab dose was 700 mg (per the economic model); and
- the average number of doses of maintenance therapy was 10.6 for obinutuzumab and 10.2 for rituximab, based on the GALLIUM trial.

^b Stated to have been ‘validated’ at the Roche Haematology Advisory Board meeting in February 2017 (Advisory Board Minutes February 2017); actual source was unclear.

^c Source was Australian market research comprising the results of interviews/online self-complete surveys with 29 haematologists between March to June 2017 (Metis Healthcare Research 2017). The question asked was “█”

█ The responses were: R-Chemo + maintenance = █%; R-chemo without maintenance = █%. (source: Metis Healthcare Research 2017, attachment to November 2017 submission, page 5.

- 4.15 The resubmission stated that the proportion of patients likely to receive maintenance therapy would be “█% for obinutuzumab (inclusive of patients who will receive obinutuzumab + bendamustine induction followed by obinutuzumab maintenance) and █% for rituximab (accounting for patients unable to receive rituximab maintenance after rituximab + bendamustine induction)”.
- 4.16 Thus the resubmission assumed that the net difference (█%) represented the proportion of patients likely to receive obinutuzumab + bendamustine followed by obinutuzumab maintenance who would otherwise have received rituximab + bendamustine induction alone (no PBS-subsidised maintenance therapy).
- 4.17 The PBAC noted that the different proportions (█% versus █%) were derived from different sources, with different survey participants and methodology (including the questions asked), not solely the different drugs. Thus the PBAC considered that the resubmission’s estimates were not reliable.
- 4.18 The resubmission further justified the █% difference by stating that uptake of obinutuzumab + bendamustine followed by obinutuzumab maintenance (as a proportion of all obinutuzumab + chemotherapy use) may be low due to safety concerns. The resubmission quoted the November 2017 PBAC comments:

“The PBAC noted that 57% of patients in the GALLIUM trial received bendamustine, and that among the various chemotherapy regimens treatment with obinutuzumab + bendamustine was associated with higher rates of grade 3 to 5 infection and second neoplasm during the maintenance and follow-up phases (Marcus et al 2017). The PBAC considered that it may be appropriate for safety reasons to restrict the use of obinutuzumab to a non-bendamustine chemotherapy regimen.” (Paragraph 2.2, obinutuzumab PSD, November 2017).

- 4.19 The PBAC noted that, in the current algorithm (i.e. where only rituximab is available), it was estimated that █% of patients would not receive maintenance. The PBAC considered that a major reason that patients do not currently receive maintenance is because they received rituximab + bendamustine induction, rather than because they were unfit for maintenance.
- 4.20 The PBAC considered that most of the patients who currently receive rituximab + bendamustine would, under the proposed algorithm (i.e. where both obinutuzumab and rituximab are available) instead receive obinutuzumab + bendamustine followed by maintenance. As such, the PBAC considered that the only patients who would not receive maintenance (under the proposed treatment algorithm) would be those who are unfit for therapy e.g. due to poor performance status or older age or when clinicians and patients considered that the increased risk of infections outweighed the benefit from an incremental delay in progression. The PBAC considered that, in clinical practice few patients are unfit for maintenance following first-line induction, and most patients will elect for maintenance. In forming this view, the PBAC noted an observational study (retrospective chart review and database analysis) of patients who received rituximab maintenance or observation after induction for previously untreated follicular lymphoma. At baseline, 49 of the 51 patients (96%) had an ECOG score of 0 or 1.¹ The PBAC acknowledged the limitations of the data (e.g. there was a large proportion of missing data) but considered the study was relevant as it was based on real-world clinical practice, rather than patients enrolled in a clinical trial.
- 4.21 Thus, the PBAC considered that the resubmission’s estimate that █% of patients would not receive maintenance under the proposed algorithm, was overestimated in the context of only around 4% of patients being unfit for maintenance based on ECOG score. Further, it considered that a PBS-listing restricted to once in a lifetime as proposed by the sponsor, could encourage use of obinutuzumab maintenance after induction.
- 4.22 The PBAC noted the resubmission’s claim that some patients may not receive obinutuzumab maintenance due to the adverse events associated with

¹ Walker, Mark S. et al. “Symptom Burden and Quality of Life in Patients with Follicular Lymphoma Undergoing Maintenance Treatment with Rituximab Compared with Observation.” *Therapeutic Advances in Hematology* 2.3 (2011): 129–139. PMC. Access on 21 March 2018 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573401/pdf/10.1177_2040620711407675.pdf Web.

obinutuzumab + bendamustine followed by maintenance. However, the PBAC considered that patients at risk of adverse events with this regimen would instead be treated with obinutuzumab + another chemotherapy backbone followed by maintenance, and thus would still receive obinutuzumab maintenance.

4.23 Overall, the PBAC considered that in Australian clinical practice under the proposed restriction around 20% of patients who achieved a complete or partial response to obinutuzumab would not receive maintenance versus 39% of those who achieved a complete or partial response to rituximab. That is, around 80% of eligible patients would receive maintenance in the proposed algorithm versus █% in the current algorithm. Thus, the PBAC considered that the difference in the proportion of eligible patients receiving maintenance in the proposed versus current algorithm would be around 19% in the previously untreated setting, rather than the █% estimated by the resubmission.

Financial impact – previously untreated advanced follicular lymphoma

4.24 The table below provides a summary of estimated patient numbers, scripts and costs to the PBS/RPBS and the Government. As a minor resubmission, these changes were not evaluated.

Table 7: Estimated use and financial implications of obinutuzumab in previously untreated advanced FL

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
No. pts treated - induction	█	█	█	█	█	█
No. pts treated - maintenance	█	█	█	█	█	█
Total no. scripts	█	█	█	█	█	█
Net cost of obinutuzumab to PBS/RPBS	█	█	█	█	█	█
Less cost of substituted rituximab	█	█	█	█	█	█
Overall net cost to PBS/RPBS	█	█	█	█	█	█
Net cost to MBS	█	█	█	█	█	█
Overall net cost to Government	█	█	█	█	█	█
Previous submission (November 2017) - estimated financial implications						
Overall net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to government for MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Overall net cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Difference in estimated financial estimates compared with the previous submission						
Difference in net cost to PBS/ RPBS ^a	█	█	█	█	█	█

Source: Table 3.1, p11 of the resubmission; Table 12, 6.09 obinutuzumab PBAC Minutes, November 2017; '2a. Patients –epi' worksheet,'3a. Volumes – new', Updated Section 4 Workbook.xlsx

MBS = Medicare Benefits Schedule; No = number; PBS = Pharmaceutical Benefits Scheme; pts = patients; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Difference in net cost to Government (i.e. including MBS) was the same because there was no difference in MBS costs between the two submissions.

4.25 The resubmission estimated that obinutuzumab would be associated with an overall net saving to the PBS/RPBS of less than \$10 million over six years. This compares

with a cost of \$60 - \$100 million over six years estimated in the previous submission. The difference was due to the lower obinutuzumab price (reduced the financial impact) and the inclusion of differential use of maintenance therapy between the arms (increased the financial impact). The PBAC considered that the cost to the PBS/RPBS was underestimated as the resubmission had underestimated the proportion of additional patients who would receive maintenance with obinutuzumab. When MBS costs were included this changed to a net cost of less than \$10 million over six years (cost to MBS/PBS/RPBS). The MBS costs were unchanged since the previous submission. They were based on each patient requiring two additional MBS infusions with obinutuzumab relative to rituximab, to account for the additional two antibody doses required during induction (i.e. obinutuzumab is dosed on Days 1, 8 and 15 of Cycle 1, while rituximab is dosed only on Day 1 of Cycle 1). The PBAC noted that the resubmission did not include the MBS costs associated with the additional obinutuzumab maintenance infusions that would be required.

4.26 Further, the resubmission did not include the cost of treating adverse events associated with obinutuzumab. The previous PBAC minutes had noted that obinutuzumab was associated with a higher incidence of serious infusion-related reactions and serious cardiac events (paragraph 7.8, obinutuzumab PSD, November 2017). Inclusion of these costs would further increase the cost to Government.

4.27 Sensitivity analyses conducted during preparation of the minor overview are presented in the table below.

Table 8: Sensitivity analyses: Overall net cost to the PBS/RPBS of obinutuzumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case (presented in resubmission)						
Overall net cost to PBS/RPBS	██████	██████	██████	██████	██████	██████
Higher incremental use of obinutuzumab maintenance (base case: █████% in obinutuzumab arm; █████% rituximab arm)						
70% obinutuzumab arm; 50% rituximab arm	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Reduction to price of rituximab (base case: PBS price on 1 Feb 2018)						
Further 16% reduction to rituximab price	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████

Source: compiled during preparation of the minor overview based on 'Updated Section 4 Workbook.xlsx'

Rituximab-refractory follicular lymphoma

4.28 The resubmission did not estimate the financial impact of listing obinutuzumab in rituximab-refractory follicular lymphoma. During preparation of the minor overview, the updated drug cost for obinutuzumab was applied to the financial estimates submitted in November 2016 for rituximab-refractory follicular lymphoma. No other changes were made to the model; the results are presented in the table below. The PBAC noted that this analysis was provided for indicative purposes only.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
With updated obinutuzumab drug costs (no other changes were made to the financial estimates) ^a						
Net cost to PBS/RPBS ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Base case presented in November 2016						
Net cost to PBS/RPBS ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Based on 'Financial cost to PBS.xlsx' spreadsheet submitted in November 2016. *Ital* = figures in italics were calculated or included during preparation of the minor overview

^a Cells C50 and C47 of 'Background and Assumptions' worksheet were changed to \$ [REDACTED] (weighted DPMA) and \$ [REDACTED] (AEMP), respectively

^b Net cost to PBS/RPBS less patient copayments and including PBS/RPBS offsets

4.29 When the obinutuzumab drug costs were reduced from \$ [REDACTED] to \$ [REDACTED] (AEMP) in the November 2016 financial estimates for rituximab-refractory follicular lymphoma, the net cost to the PBS/RPBS almost halved from more than \$100 million over six years to \$30-\$60 million. The ESC advised for the November 2016 submission that the number of eligible patients may have been underestimated as the submission did not use a robust method to take into consideration of both the prevalent and incident population of rituximab-refractory patients follicular lymphoma population in Australia.

4.30 Examples of other potential issues with estimating the financial impact in the rituximab-refractory setting included:

- the financial estimates would need to include the impact of listing obinutuzumab in the previously untreated setting, which would reduce the use in the rituximab-refractory setting over time (given once in a lifetime use was proposed); and
- the price of bendamustine was based on the PBS-listed price in the previously untreated iNHL setting. However, the price in the rituximab-refractory setting is not known, as it is not PBS-listed in this setting.

Financial management – risk sharing arrangements

4.31 The resubmission did not propose a risk sharing arrangement stating that there was no additional impact on PBS budget. However, the PBAC considered that an additional budget impact would be associated with the listing of obinutuzumab in rituximab-refractory follicular lymphoma.

4.32 Further, the proposed restrictions may also allow use in broader populations than intended as the current wording may allow use in combination with chemotherapy regimens other than bendamustine in the rituximab-refractory setting.

4.33 Rituximab has a weighted price across several indications. The submission used an AEMP per mg of \$3.65 based on the published price. The actual AEMP per mg of rituximab for previously untreated follicular lymphoma is \$ [REDACTED] for induction and \$ [REDACTED] for maintenance.

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

5 PBAC Outcome

- 5.1 The PBAC deferred making a decision regarding the listing of obinutuzumab for previously untreated advanced follicular lymphoma (Stage II bulky or Stage III/IV) and rituximab-refractory follicular lymphoma to allow further work to establish a price for treatment with obinutuzumab that could be considered cost-effective in both these follicular lymphoma settings. The PBAC also considered that for both treatment settings, the financial impact was uncertain. In the previously untreated setting, the resubmission had underestimated the amount of additional use of maintenance therapy, and no financial estimates had been provided for the rituximab-refractory follicular lymphoma setting.
- 5.2 The PBAC noted that the resubmission requested listing in two different stages of follicular lymphoma: previously untreated and rituximab-refractory. The PBAC considered that it was important to assess the two settings concurrently as listing in only one may be inequitable. In particular, if obinutuzumab was listed for previously untreated patients only, then prevalent patients (who would have already received first-line induction with rituximab) would be ineligible for PBS-subsidised obinutuzumab at any stage of their follicular lymphoma.
- 5.3 The PBAC noted that limiting use of obinutuzumab to once per lifetime cannot be administered in a Streamlined Authority listing, whereas it can be via an Authority Required – Telephone restriction. Therefore, the PBAC considered that an Authority Required – Telephone restriction would be appropriate. The PBAC noted the restriction level would not align with rituximab, but considered this difference was appropriate given the substantial risk of re-use of obinutuzumab.
- 5.4 The PBAC considered that separate restrictions would be required for the previously untreated and rituximab-refractory settings given the different dosage regimens. Further, the PBAC considered that a grandfather restriction would be appropriate and recommended that the grandfather restriction be consistent with the PBS population for obinutuzumab.

Previously untreated advanced follicular lymphoma

- 5.5 The PBAC considered that flow on changes would be required to the bendamustine restriction to facilitate use of obinutuzumab + bendamustine in previously untreated follicular lymphoma. Specifically, the PBAC considered that the bendamustine PBS-listing (which is currently for induction therapy in previously untreated stage III or IV indolent CD20 positive non-Hodgkin's lymphoma, in combination with rituximab) should be expanded to include: treatment in combination with obinutuzumab; and use in stage II bulky CD20 positive follicular lymphoma.
- 5.6 The PBAC recalled its previous concerns that obinutuzumab was associated with an uncertain magnitude of OS benefit over rituximab and an inferior comparative safety profile, particularly in patients ≥ 65 years of age and also with the regimen of

obinutuzumab + bendamustine followed by maintenance therapy. The PBAC further recalled its previous concerns that the clinical need for obinutuzumab in the previously untreated setting may be limited to a small sub-group of patients who would be difficult to identify on a biological basis (i.e. those able to tolerate its increased toxicity, and who would not optimally respond to rituximab-based regimens). The PBAC considered that these issues were adequately addressed through the resubmission's proposal to limit obinutuzumab use to once per lifetime. As such, clinical judgement could be used to determine the setting in which obinutuzumab would have the more favourable risk-benefit profile in each individual patient.

- 5.7 The PBAC noted that the resubmission proposed a price for obinutuzumab that aimed to result in a [REDACTED]. [REDACTED] The PBAC noted that with the obinutuzumab price proposed, the sponsor's model indicated a dominant ICER (i.e. more effective and less costly than the comparator).
- 5.8 The PBAC noted that the obinutuzumab price proposed in the resubmission attempted to account for differences in the proportion of patients who would receive maintenance therapy. The PBAC noted that the resubmission estimated that [REDACTED]% of patients with a complete or partial response to obinutuzumab would not receive obinutuzumab maintenance versus [REDACTED]% for rituximab (accounting for patients unable to receive rituximab maintenance because they had received rituximab + bendamustine induction), and so assumed there would be a [REDACTED]% increase in maintenance use among eligible patients if obinutuzumab were listed. The PBAC noted that the two proportions ([REDACTED]% versus [REDACTED]%) were derived from different sources with different methodology and thus considered the comparison was not reliable.
- 5.9 The PBAC considered that a major reason that responding patients do not currently go on to receive maintenance therapy is because they received rituximab + bendamustine induction. The PBAC considered that, if obinutuzumab were available under the proposed algorithm with a once-in-a-lifetime restriction, the only patients who would not receive maintenance would be those who are unfit for therapy (e.g. due to poor performance status or older age or at high risk of infection). The PBAC considered that few patients are unfit for maintenance following first-line induction in clinical practice, and most patients will elect for maintenance. In forming this view, the PBAC noted an observational study of patients who had undergone induction for previously untreated follicular lymphoma. At baseline, 96% had an ECOG score of 0 or 1. Thus, the PBAC considered that the resubmission's estimate that [REDACTED]% of patients would not receive obinutuzumab maintenance was overestimated in the context of only around 4% of patients being unfit for maintenance based on ECOG score. Further, it considered that a PBS-listing

restricted to once in a lifetime as proposed by the sponsor, could encourage use of obinutuzumab maintenance after induction.

- 5.10 Overall, the PBAC considered that it would be more realistic to assume that, in Australian clinical practice under the proposed restriction, around 20% of patients who achieved a complete or partial response to obinutuzumab would not receive maintenance versus 39% of those who achieved a complete or partial response to rituximab. The PBAC considered that the financial estimates and economic analysis should be revised to reflect these proportions.
- 5.11 As outlined above, the PBAC considered that the cost to the PBS/RPBS was underestimated as the resubmission had underestimated the number of additional patients who would receive maintenance with obinutuzumab.

Rituximab-refractory follicular lymphoma

- 5.12 The PBAC considered that there was an unmet clinical need for additional PBS-subsidised medicines for the treatment of rituximab-refractory follicular lymphoma.
- 5.13 The PBAC noted that the resubmission proposed obinutuzumab be used in combination with bendamustine in the rituximab-refractory re-induction setting, but that bendamustine is not currently PBS-listed in this setting. The PBAC noted that the only evidence presented for bendamustine combination therapy in this setting was the GADOLIN trial (obinutuzumab + bendamustine versus bendamustine monotherapy). In recognising the clinical need for additional treatments in this setting, the PBAC indicated that it would consider listing bendamustine, for use in combination with obinutuzumab, in rituximab-refractory follicular lymphoma.
- 5.14 The PBAC noted that the resubmission did not provide a basis for establishing the comparative cost-effectiveness of obinutuzumab in rituximab-refractory follicular lymphoma. Instead, the resubmission proposed that obinutuzumab [REDACTED].
- 5.15 The PBAC noted that when the proposed obinutuzumab drug cost was applied to the November 2016 economic model for rituximab-refractory follicular lymphoma, the ICER was \$15,000/QALY-\$45,000/QALY.
- 5.16 However, the PBAC recalled that it previously (November 2016) did not accept the submission's use of the cost of bendamustine as a proxy for the cost of best supportive care, given that bendamustine monotherapy was previously considered not to be cost-effective in this setting. The PBAC re-iterated this concern and considered as an alternative that the cost of bendamustine could be replaced with the cost of CHOP i.e. for cost inputs, the economic model should compare the cost of obinutuzumab + bendamustine (followed by obinutuzumab maintenance) versus CHOP without maintenance.
- 5.17 The PBAC noted the resubmission proposed the [REDACTED]. The PBAC considered

that, given the uncertainties it had previously noted in November 2016 with the economic evaluation for the rituximab-refractory setting (which included the extrapolation of immature trial data and the use of an inappropriate time horizon), the price of obinutuzumab in this setting should not be higher than in the previously untreated setting.

- 5.18 The PBAC noted that the resubmission did not estimate the financial impact of listing obinutuzumab in rituximab-refractory follicular lymphoma. The PBAC considered that revised financial estimates would be required given the listing would have financial implications to the PBS/RPBS. The PBAC considered the revised financial estimates should take into account the impact of listing obinutuzumab in the previously untreated setting (given once per lifetime use was proposed).
- 5.19 The PBAC noted that the resubmission did not propose a risk sharing arrangement stating that there was no additional impact to the PBS. However, the PBAC considered that there would be a financial impact for listing in the rituximab-refractory setting. The PBAC foreshadowed that a risk sharing arrangement may be required if there was substantial uncertainty in the revised financial estimates.

Both treatment settings

- 5.20 The PBAC considered that the purpose of the deferral was to allow time to:
- update the restrictions, including providing separate restrictions for the two treatment settings;
 - in the previously untreated setting: update the proportion of patients eligible for obinutuzumab maintenance (a difference of █% should be used, rather than █%) in both the financial and economic analyses and include the MBS costs associated with the additional obinutuzumab maintenance infusions in the financial estimates; and
 - in the rituximab-refractory setting: update the cost inputs in the economic model to compare the cost of obinutuzumab + bendamustine (followed by obinutuzumab maintenance) versus CHOP; and update the financial estimates to include the impact of listing obinutuzumab in the previously untreated setting (which would reduce the use in the rituximab-refractory setting over time).
- 5.21 The PBAC noted that this resubmission is not eligible for an Independent Review as it has been deferred.

Outcome:

Deferred

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

Roche is committed to working with the Department of Health and the PBAC to enable access to obinutuzumab for people with advanced follicular lymphoma

Addendum to the March 2018 PBAC Minutes:

11. OBINUTUZUMAB, Solution for I.V. infusion, 1000 mg in 40 mL, GAZYVA[®], Roche Pty Ltd

8 PBAC Outcome

- 8.1 At its special meeting on 20 April 2018, the PBAC recommended extending the PBS-listing of obinutuzumab as a Section 100 Efficient Funding of Chemotherapy benefit to include the treatment of patients with previously untreated advanced follicular lymphoma (Stage II bulky or Stage III/IV) and rituximab-refractory follicular lymphoma. In the previously untreated setting the recommendation was made on the basis that the price for obinutuzumab would result in a “cost-neutral” listing (i.e. a price that would result in no additional PBS expenditure versus current PBS expenditure on rituximab in this setting). In the rituximab-refractory setting, the recommendation was made on the basis of acceptable cost-effectiveness compared with best supportive care.
- 8.2 The PBAC re-iterated its previous consideration that obinutuzumab use should be limited to once per lifetime, in either the previously untreated or rituximab-refractory follicular lymphoma setting.
- 8.3 The PBAC considered that the restrictions for use in the maintenance settings should include the following criteria “Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition (rather than the text outlined in Paragraph 2.6 of the March 2018 obinutuzumab Public Summary Document (PSD)).
- 8.4 The PBAC noted the additional information that was provided by the sponsor subsequent to the March 2018 consideration, which is outlined below. The PBAC considered that these changes had adequately addressed its previous concerns.
- 8.5 In the previously untreated setting:

- the proportion of patients eligible for obinutuzumab maintenance was updated (a difference of 19% between the current and proposed algorithm was used as requested) in both the financial and economic analyses;
- a reduced price was proposed (6% reduction compared with the resubmission considered in March 2018) which meant that cost neutrality was maintained in the previously untreated setting with the revised proportion using obinutuzumab maintenance; and
- the MBS costs associated with the additional obinutuzumab maintenance infusions were included in the financial estimates.

The PBAC considered that, with these changes, the resubmission had proposed a price for obinutuzumab that resulted in a “cost-neutral” listing in the previously untreated setting. While the PBAC noted that the March 2018 minor submission had included an economic model, the PBAC re-iterated its consideration from November 2017 that the cost-effectiveness against rituximab was highly uncertain in the previously untreated setting, as the economic model assumed an advantage in survival based on delayed disease progression that was unable to be fully tested due to immature OS data (Paragraph 7.1, obinutuzumab PSD, November 2017).

8.6 The results from the updated financial estimates are provided in the table below.

Table 10: Estimated use and financial implications of obinutuzumab in previously untreated FL - addendum

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
No. pts treated – induction (initiators)						
No pts treated – maintenance (initiators)						
Total no. scripts						
Net cost of obinutuzumab to PBS/RPBS	\$	\$	\$	\$	\$	\$
Less cost of substituted rituximab	-\$	-\$	-\$	-\$	-\$	-\$
Overall net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Additional IV infusions required ^a						
Net cost to MBS	\$	\$	\$	\$	\$	\$
Overall net cost to Government	-\$	-\$	\$	\$	\$	\$

Source: '2b. 1L FL_Updated Section 4 Workbook_April 18 PBAC.xlsx'

MBS = Medicare Benefits Schedule; No = number; PBS = Pharmaceutical Benefits Scheme; pts = patients; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Using MBS item 13918, IV infusion > 1 hour. Based on net change in prescription volumes (induction and maintenance) in the April 2018 estimates. (It was based only on the net change in prescription volumes for induction in the March 2018 estimates)

8.7 The PBAC noted that, given the new price proposed, the sponsor estimated that obinutuzumab would be associated with an overall net saving to the PBS/RPBS of less than \$10 million over six years (versus a saving of less than \$10 million over six years in the March 2018 submission). The PBAC considered that this indicated that obinutuzumab was cost-neutral compared with rituximab in the previously untreated setting (i.e. the price resulted in no additional PBS expenditure versus current PBS expenditure on rituximab in this setting).

8.8 In the rituximab-refractory setting:

- the reduced price proposed for the previously untreated setting (6% reduction compared with the resubmission considered in March 2018) was applied in both the financial and economic analyses;
- the cost inputs in the economic model were updated to compare the cost of obinutuzumab + bendamustine (followed by obinutuzumab maintenance) versus CHOP; and
- the financial estimates were updated to include the impact of listing obinutuzumab in the previously untreated setting (which would reduce the use in the rituximab-refractory setting over time).

8.9 The results from the updated economic model are provided in the table below.

Table 11: Results of the economic evaluation for rituximab-refractory follicular lymphoma - addendum

Step and component	Obinutuzumab + bende	Best supportive care (CHOP)	Increment
Updated model – April 2018 Special meeting			
Costs	\$ [REDACTED] ^a	\$ [REDACTED]	\$ [REDACTED]
QALY	4.38	3.00	1.38
Incremental cost/QALY			\$ [REDACTED]

Source: '3a. rrFL_Updated Economic Evaluation_April 18 PBAC.xlsx', Table 5 PBAC Minutes obinutuzumab

QALY = quality-adjusted life year;

^a The bendamustine cost in the obinutuzumab + bendamustine arm was \$1,533 (DPMA weighted across public and private use), based on the current listing (per the financial estimates). The PBAC noted that, using the cost of CHOP as a proxy for best supportive care and the revised obinutuzumab drug cost, the updated base case ICER was \$15,000 - \$45,000 per QALY. The PBAC again recalled that, in November 2016, it had considered that the ICER was highly uncertain and was likely to be significantly underestimated, however considered that the cost-effectiveness of obinutuzumab in this setting was acceptable at the price proposed in the addendum.

8.10 The results from the updated financial estimates for rituximab-refractory follicular lymphoma are provided in the table below.

Table 12: Estimated use and financial implications of listing obinutuzumab in the rituximab-refractory setting - addendum

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated patients – obinutuzumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Induction ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Maintenance ^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Treated patients – bendamustine	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts - obinutuzumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts – bendamustine ^c	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS – obinutuzumab	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS – bendamustine ^d	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS – both drugs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 10, p24 Obinutuzumab PBAC Minutes, November 2016; 3b. rrFL_Updated Financial Cost to PBS_April 18 PBAC.xlsx'

^a The key change to the financial estimates was that 48% of newly diagnosed patients who undergo first-line induction were assumed to use obinutuzumab (in the previous submission, 100% were assumed to receive rituximab-based first-line induction). Thus, the financial estimates assumed that 5% of all incident patients would be 'fast progressers' following first-line rituximab (versus 11% in the November 2016 submission) and 7% would be 'eventual progressers' following first-line rituximab who take four years to progress (versus 12% in the November 2016 submission).

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^b Total number of patients treated each year with maintenance therapy (includes patients continuing from the previous year) for consistency with reporting in the November 2016 PBAC Minutes.

^c One script was assumed to be used for every two doses of bendamustine (administered as 90mg/m² on Days 1 and 2 of a 28 day cycle for up to 6 cycles), *which may not be appropriate and does not align with the Secretariat's proposed listing for bendamustine.*

^d Net cost to the PBS included the cost of bendamustine of \$1,533 (DPMA weighted across public and private use), based on the current listing.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

- 8.11 The estimated cost to the PBS/RPBS of listing obinutuzumab plus bendamustine was \$20 - \$30 million over six years. Of this \$10 - \$20 million over six years was estimated to be for obinutuzumab and \$10 - \$20 million for bendamustine.
- 8.12 The PBAC noted that the addendum's revised financial estimates added an assumption that 48% of newly diagnosed patients who undergo first-line induction would use obinutuzumab. This assumption was applied from Year 1 of listing, which almost halved the number of patients. However, the PBAC considered that the first-line listing would not substantially impact use in the rituximab-refractory setting until the incident pool of patients (who had the opportunity to receive obinutuzumab first-line) become refractory; while some patients would become refractory quickly, others would progress more slowly. Thus reductions in later-line obinutuzumab use would be likely to occur more gradually over time. The PBAC considered that this may have underestimated patient numbers.
- 8.13 The PBAC noted that the sponsor had requested that the restriction for rituximab-refractory maintenance therapy, as outlined in Section 2, should be amended to include patients with stable disease following re-induction, which the sponsor stated would be in line with the GADOLIN trial. The PBAC considered that it is probable that the incremental benefit of obinutuzumab maintenance in patients with stable disease would be small and noted that other treatment options exist. The PBAC also noted that it would be inconsistent with the definition of refractory, as applied to rituximab, to consider a patient suitable for obinutuzumab maintenance if there has been no response to obinutuzumab-containing regimen. Therefore, the PBAC advised that obinutuzumab maintenance should be reserved for those patients with partial or complete response to re-induction treatment.
- 8.14 The PBAC considered that in the rituximab-refractory setting, there was a high risk of use outside the intended population in patients who are not truly refractory to rituximab. Therefore, the PBAC advised that a Risk Sharing Arrangement (RSA) with a hard cap would be required for obinutuzumab in the rituximab-refractory setting.
- 8.15 As part of this consideration, the PBAC also recommended extending the PBS-listing of bendamustine as a Section 100 Efficient Funding of Chemotherapy benefit to include the treatment of patients with rituximab-refractory follicular lymphoma in combination with obinutuzumab. The PBAC recommended that this be a separate listing in order to monitor bendamustine usage across the different settings.

- 8.16 The PBAC also recommended amendments to the current bendamustine restriction for previously untreated follicular lymphoma to allow use in combination with obinutuzumab.

9 Recommended listing

Amend existing/recommended listing as follows:

Induction setting – previously untreated

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	9	GAZYVA® Roche Products Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Severity:	Stage II bulky or Stage III/IV		
Condition:	Follicular lymphoma		
PBS Indication:	Stage II bulky or Stage III/IV follicular lymphoma		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone		
Treatment phase:	Induction treatment		
Clinical criteria:	The condition must be CD20 positive, AND The condition must be previously untreated, AND The condition must be symptomatic, AND The treatment must be for induction treatment purposes only. AND The treatment must be in combination with chemotherapy, AND The treatment must not exceed 10 doses for induction treatment with this drug for this condition		

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Prescriber Instructions	A patient may only qualify for PBS-subsidised initiation treatment once in a lifetime under: <ol style="list-style-type: none"> 1. the previously untreated induction treatment restriction; or 2. the rituximab-refractory re-induction restriction; or 3. the previously untreated grandfather restriction; or 4. the rituximab-refractory grandfather restriction.
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

Rituximab-refractory re-induction setting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	7	GAZYVA® Roche Products Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Condition:	Follicular lymphoma		
PBS Indication:	Follicular lymphoma		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone		
Treatment phase:	Re-induction treatment		
Clinical criteria:	<p>The patient must not have previously received PBS-subsidised obinutuzumab, AND The condition must be CD20 positive, AND The condition must be refractory to treatment with rituximab for this condition, AND The condition must be symptomatic, AND The treatment must be for re-induction treatment purposes only, AND The treatment must be in combination with bendamustine, AND The treatment must not exceed 8 doses for re-induction treatment with this drug for this condition</p>		
Prescriber Instructions	<p>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</p> <p>A patient may only qualify for PBS-subsidised initiation treatment once in a lifetime under:</p> <ol style="list-style-type: none"> 1. the previously untreated induction treatment restriction; or 		

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	<p>2. the rituximab-refractory re-induction restriction; or</p> <p>3. the previously untreated grandfather restriction; or</p> <p>4. the rituximab-refractory grandfather restriction.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Maintenance therapy - previously untreated setting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	5	GAZYVA® Roche Products Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Severity:	Stage II bulky or Stage III/IV		
Condition:	Follicular lymphoma		
PBS Indication:	Stage II bulky or Stage III/IV follicular lymphoma		
Treatment phase:	Maintenance therapy		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone		
Treatment criteria:	<p>Patient must have previously received PBS subsidised treatment with this drug under the previously untreated initial restriction, OR Patient must have previously received PBS subsidised treatment with this drug under the previously untreated grandfather restriction, AND The condition must be CD20 positive, AND Patient must have demonstrated a partial or complete response to PBS-subsidised induction treatment with this drug for this condition AND The treatment must be maintenance therapy, AND The treatment must be the sole PBS-subsidised treatment for this condition, AND The treatment must not exceed 12 doses or 2 years duration of treatment, whichever comes first, under this restriction, AND Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>		
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Special Pricing Arrangements apply.</p>		

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Maintenance therapy – rituximab-refractory setting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	5	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Follicular lymphoma
PBS Indication:	Follicular lymphoma
Treatment phase:	Maintenance therapy
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	<p>Patient must have previously received PBS subsidised treatment with this drug under the rituximab refractory initial restriction, OR Patient must have previously received PBS subsidised treatment with this drug under the rituximab refractory grandfather restriction, AND The condition must be CD20 positive, AND The condition must have been refractory to treatment with rituximab, AND Patient must have demonstrated a partial or complete response to PBS-subsidised re-induction treatment with this drug for this condition, AND The treatment must be maintenance therapy, AND The treatment must be the sole PBS subsidised treatment for this condition, AND The treatment must not exceed 12 doses or 2 years duration of treatment, whichever comes first, under this restriction, AND Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.</p>

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Grandfathering previously untreated setting - induction or maintenance

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	9	GAZYVA® Roche Products Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Severity:	Stage II bulky or Stage III/IV		
Condition:	Follicular lymphoma		
PBS Indication:	Stage II bulky or Stage III/IV follicular lymphoma		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone		
Treatment phase:	Grandfather treatment -- previously untreated setting		
Treatment criteria:	<p>The patient must have received non-PBS subsidised treatment with this drug for this condition prior to [Listing date] AND The condition must be CD20 positive, AND The condition must have been untreated prior to initiating non-PBS subsidised treatment with this drug for this condition. AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND The treatment must be in combination with chemotherapy for induction treatment AND The treatment must not exceed 10 doses for induction treatment with this drug for this condition OR The patient must have demonstrated a partial or complete response to induction treatment with this drug for this condition for maintenance treatment AND The treatment must be the sole PBS subsidised treatment for maintenance treatment AND The treatment must not exceed 12 doses or 2 years duration of maintenance treatment, whichever comes first</p>		
Prescriber Instructions	<p>A patient may only qualify for PBS-subsidised initiation treatment once in a lifetime under:</p> <ol style="list-style-type: none"> 1. the previously untreated induction treatment restriction; or 2. the rituximab-refractory re-induction restriction; or 3. the previously untreated grandfather restriction; or 4. the rituximab-refractory grandfather restriction. 		

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Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.
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Grandfathering Rituximab-refractory re-induction and maintenance setting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	7	GAZYVA® Roche Products Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Condition:	Follicular lymphoma		
PBS Indication:	Follicular lymphoma		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone		
Treatment phase:	Grandfather treatment – rituximab refractory		
Treatment criteria:	<p>The patient must have received non-PBS subsidised treatment with this drug for this condition prior to [Listing date] AND The condition must be CD20 positive, AND The condition must have been refractory to treatment with rituximab prior to initiating non-PBS treatment this drug for this condition AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND The treatment must be in combination with bendamustine for re-induction treatment AND The treatment must not exceed 8 doses for re-induction treatment with this drug for this condition OR The patient must have demonstrated a partial or complete response to re-induction treatment with this drug for this condition AND The treatment must be the sole PBS subsidised treatment for maintenance treatment AND The treatment must not exceed 12 doses or 2 years duration of maintenance treatment, whichever comes first</p>		
Prescriber Instructions	<p>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</p> <p>A patient may only qualify for PBS-subsidised initiation treatment once in a lifetime under:</p>		

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	<ol style="list-style-type: none"> 1. the previously untreated induction treatment restriction; or 2. the rituximab-refractory re-induction restriction; or 3. the previously untreated grandfather restriction; or 4. the rituximab-refractory grandfather restriction.
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.</p>

Bendamustine restrictions

Update to existing bendamustine listing in the previously untreated induction setting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BENDAMUSTINE powder for injection 100 mg powder for injection 25 mg	200 mg	11	Ribomustin® Janssen-Cilag Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS Indication:	Previously untreated <u>Stage II bulky</u> or stage III or IV indolent non-Hodgkin's lymphoma
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Streamlined
Treatment phase:	Induction treatment
Treatment criteria:	<p>The condition must be CD20 positive, AND The condition must be previously untreated, AND The condition must be symptomatic, AND The treatment must be for induction treatment purposes only, AND The treatment must be in combination with rituximab or <u>obinutuzumab</u>, AND The treatment must not exceed 6 cycles (12 doses) with this drug under this restriction</p>
Administrative Advice	No increase in the maximum number of repeats may be authorised.

New listing for bendamustine in the rituximab-refractory re-induction setting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
BENDAMUSTINE powder for injection 100 mg powder for injection 25 mg	200 mg	11	Ribomustin® Janssen-Cilag Pty Ltd
Category / Program	Section 100 – Efficient funding of Chemotherapy		
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners		
Condition:	Follicular lymphoma		
PBS Indication:	Follicular lymphoma		
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined		
Treatment phase:	Re-induction treatment		
Treatment criteria:	The condition must be CD20 positive, AND The condition must be refractory to treatment with rituximab for this condition, AND The condition must be symptomatic, AND The treatment must be for re-induction treatment purposes only, AND The treatment must be in combination with obinutuzumab, AND The treatment must not exceed 6 cycles (12 doses) with this drug under this restriction.		
Prescriber Instructions	The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.		
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.		

10 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

11 Sponsor's Comment

The sponsor had no comment.