6.09 OBINUTUZUMAB, Solution for I.V. infusion 1000 mg in 40 mL, Gazyva®, Roche Products Pty Ltd

1 Purpose of application

1.1 Section 100 Efficient Funding of Chemotherapy listing for obinutuzumab for treatment of previously untreated advanced follicular lymphoma (stage II bulky or stage III/IV). While obinutuzumab has been considered previously by the PBAC, this is the first submission for first-line treatment of advanced follicular lymphoma.

1.2 The submission sought listing on the basis of a cost-utility analysis compared to rituximab.

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

Component	Description
Population	Patients with previously untreated advanced follicular lymphoma (stage II bulky or stage III/IV CD20 positive follicular lymphoma).
Intervention	Obinutuzumab in combination with chemotherapy as induction treatment followed by obinutuzumab maintenance monotherapy.
Comparator	Rituximab in combination with chemotherapy as induction treatment followed by rituximab maintenance monotherapy.
Outcomes	PFS; OS; QoL (as measured by FACT-Lym and EQ-5D); treatment-related AEs.
Clinical claim	In patients with previously untreated advanced follicular lymphoma, obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy is superior in effectiveness in terms of PFS (investigator-assessed and independently assessed) and inferior in safety compared to rituximab plus chemotherapy induction therapy and rituximab maintenance monotherapy. The submission also claimed that OS data from obinutuzumab were supportive of the PFS endpoint.

AEs=adverse events; EQ-5D=EuroQoL five dimension questionnaire; FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma questionnaire; OS=overall survival; PFS=progression-free survival; QoL=quality of life
Source: Table 1.1.1 p2-3 of the submission.

2 Requested listing

2.1 The requested PBS listing for both induction and maintenance therapy of obinutuzumab as well as the requested grandfathering restriction are provided below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OBINUTUZUMAB Solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	9	Published Public: $5,376.22 Private: $5,488.40 Effective Public: $[redacted] Private: $[redacted]	GAZYVA® Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Previously untreated
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*
Treatment phase:	Induction treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☒Streamlined
Treatment criteria:	*The condition must be symptomatic*~~Patient must require treatment~~, AND The condition must be previously untreated, AND The treatment must be in combination with *PBS-subsidised* chemotherapy, AND *The treatment must be for 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.
Clinical criteria:	-
Population criteria:	-
Prescriber Instructions	-
Administrative Advice	*A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.* No increase in the maximum number of repeats may be authorised *Special Pricing Arrangements apply*

Name, Restriction, Manner of administration and form	Max. Qty	№.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	5	Published Public: $5,376.22 Private: $5,488.40 Effective Public: $[redacted] Private: $[redacted]	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	~~Previously untreated~~
Severity:	Stage II bulky or Stage III/IV ~~disease~~
Condition:	CD20 positive follicular lymphoma
PBS Indication:	~~*Previously untreated*~~ *Stage II bulky or Stage III/IV* ~~*disease*~~ *CD20 positive follicular lymphoma*
Treatment phase:	Maintenance therapy
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☒Streamlined
Treatment criteria:	The treatment must be as monotherapy, AND The treatment must be ~~for~~ maintenance therapy ~~only,~~ AND Patient must have demonstrated a partial or complete response to the PBS-subsidised *obinutuzumab and chemotherapy* induction treatment, AND Patient must not have progressive disease while receiving treatment with this drug, AND Patient must not receive more than 12 doses or 2 years duration of treatment, whichever comes first, under this restriction.
Clinical criteria:	-
Population criteria:	-
Prescriber Instructions	-
Administrative Advice	*A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.* *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply*

Name, Restriction, Manner of administration and form	Max. Qty	№.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	~~9~~*8*	Published Public: $5,376.22 Private: $5,488.40 Effective Public: $[redacted] Private: $[redacted]	GAZYVA®	Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Previously untreated
Severity:	Stage II bulky or Stage III/IV ~~disease~~
Condition:	CD20 positive follicular lymphoma
PBS Indication:	*Previously untreated Stage II bulky or Stage III/IV ~~disease~~ CD20 positive follicular lymphoma*
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☒Streamlined
Treatment criteria:	Patient must have received treatment with obinutuzumab for this condition prior to the [PBS listing date], AND The treatment must be in combination with *PBS-subsidised* chemotherapy, *AND* *The treatment must be for 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.
Clinical criteria:	-
Population criteria:	-
Prescriber Instructions	-
Administrative Advice	*A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.* No increase in the maximum number of repeats may be authorised *Special Pricing Arrangements apply*

2.2 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.

2.3 The PBAC noted that the utilisation of obinutuzumab as maintenance after obinutuzumab and bendamustine induction would not be consistent with the current bendamustine restrictions, in which no maintenance is allowed. Hence flow-on changes would be required for the bendamustine restriction if treatment in combination with obinutuzumab was recommended.

2.4 The PBAC considered that, although not stated in the rituximab listing, the restriction for maintenance therapy should include the criteria 'The treatment must be as monotherapy' and 'Patient must not have progressive disease while receiving treatment with this drug'.

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

3 Background

Registration status

3.1 TGA status: The submission was lodged under the TGA-PBAC parallel process. An application for the use of obinutuzumab in previously untreated advanced follicular lymphoma was lodged with the TGA on 3 November 2016 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."

At the time of PBAC consideration, the TGA Clinical Evaluation Report, TGA Delegate's Overview and the resolution from the TGA Advisory Committee on Medicines (ACM) were available. The ACM agreed with the TGA Delegate and advised that obinutuzumab had an overall positive benefit-risk profile for the treatment of patients with previously untreated follicular lymphoma (Ratified TGA ACM Resolution #49 October 2017). The submission indicated (p18[1]) that TGA approval is expected in mid-November 2017.

3.2 Obinutuzumab is currently TGA registered for use in combination with chlorambucil in patients with previously untreated chronic lymphocytic leukaemia (CLL) and also in combination with bendamustine, followed by obinutuzumab maintenance, in patients with follicular lymphoma who did not respond to or progressed during treatment with rituximab or a rituximab-containing regimen.

Previous PBAC consideration

3.3 A submission for the use of obinutuzumab for the treatment of rituximab-refractory follicular lymphoma was considered by the PBAC in November 2016. The PBAC rejected this submission on the basis of uncertain cost-effectiveness and concerns about the plausibility of assumptions used in the economic model. Concerns were mainly centred around the extrapolation of

[1] Note: All page references in the commentary were based on the merged submission document received on 17 July 2017.

PFS from immature data over a longer time horizon (15 years). A 10 year time horizon was considered more appropriate by the PBAC for that indication (paragraph 7.7, November 2016 obinutuzumab Public Summary Document (PSD)).

4 Population and disease

4.1 Follicular lymphoma is a B-cell lymphoma characterised by tumour cells that appear in a circular or follicular pattern and replace the normal structure of a lymph node. It is the second most common type of non-Hodgkin's lymphoma (NHL) and constitutes approximately 20% to 30% of all cases of NHL. The disease primarily affects adults aged 50 years and over and its cause is unknown.

4.2 The disease tends to be insidious in nature and the majority of patients present with asymptomatic lymph node swelling. Patients may also have abnormal enlargement of the liver or spleen or reduction in the number of blood cells. Given the asymptomatic nature of many presentations of the disease, patients generally do not require treatment until they become symptomatic, which may take months or years.

4.3 The requested listing is for first-line treatment. The submission indicated (p1) that rituximab is the standard of care for advanced stage symptomatic follicular lymphoma in both the induction (in combination with chemotherapy) and maintenance (as monotherapy) settings. The submission argued that there remains an unmet need for a novel treatment alternative to rituximab that can prolong progression-free survival (PFS) and overall survival (OS) for previously untreated patients. The PBAC considered that the place in therapy for obinutuzumab is emerging. Given the generally good response to rituximab in the first-line setting together with the indolent nature of the disease, the PBAC considered, based on the available clinical results for obinutuzumab, that the role of obinutuzumab in the first-line setting may be limited to those patients who have a suboptimal response to rituximab-based regimes, eg. those who have a short time to progression after completion of induction and/or maintenance therapy (though, at present, there are no clearly defined biological assessments to predict this subgroup of patients a priori), and are able to tolerate its increased toxicity.

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

5 Comparators

5.1 The submission nominated rituximab in combination with chemotherapy for induction treatment and rituximab monotherapy for maintenance treatment as the main comparator.

5.2 The main arguments provided in support of this nomination were that rituximab in combination with chemotherapy is the most commonly used regimen for patients with previously untreated advanced follicular lymphoma, and rituximab maintenance therapy is subsequently used in

patients who achieve a complete or partial response to induction treatment. The submission anticipated (p8) that obinutuzumab will substitute rituximab in Australian clinical practice regardless of the chemotherapy backbone that would be used for induction treatment.

5.3 The PBAC considered the nominated comparator was appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals were from patients who wanted access to new treatment options. The patients believed that obinutuzumab had reduced side effects and was associated with better outcomes compared to standard care. The PBAC noted that the clinical evidence presented in the submission did not support patient's beliefs that obinutuzumab had reduced adverse events (AEs), but rather indicated an increase in AEs.

6.3 The PBAC noted correspondence from the Leukaemia Foundation which supported obinutuzumab as a first-line treatment for follicular lymphoma. The Leukaemia Foundation considered PBS listing of obinutuzumab would expand haematologists' treatment options, allowing therapy to be more tailored for patients. The response also recalled the results of a patient survey presented in the November 2016 submission for obinutuzumab for rituximab-refractory follicular lymphoma, where fear of relapse was a common theme for participants. The PBAC also noted correspondence from Lymphoma Australia, which highlighted that the goal of initial cancer treatment is to prevent the cancer from progressing for as long as possible. Responses from both organisations stated that obinutuzumab demonstrated a sustained benefit in PFS over rituximab and extended patients' PFS by three years over standard treatments. The PBAC noted that the consumer comments were supportive of the PBS listing of obinutuzumab as requested by the submission.

Clinical trials

6.4 The submission was based on a randomised open-label phase III trial (GALLIUM) comparing obinutuzumab+chemotherapy and rituximab+chemotherapy in patients with previously untreated advanced follicular lymphoma (N=1202). Patients in the GALLIUM trial were not allowed to switch treatment. The trial also included a group of marginal zone lymphoma (MZL) patients. The Clinical Study Report (CSR) indicated that this

population was capped at 200, and the submission noted (p41) that the trial was powered for the follicular lymphoma population and was not powered to detect statistically significant differences in the MZL patients. Trial results for the MZL population were not separately presented in the submission. MZL was also not part of the sponsor's TGA application to update indications. Therefore, the MZL population was not considered relevant to the requested PBS listing (in previously untreated follicular lymphoma) and the characteristics and results of this portion of the trial were not included in the commentary. The ESC agreed that MZL and follicular lymphoma were diseases with distinct differences in characteristics, and hence it was unlikely that use would occur in MZL under the requested PBS listing.

6.5 The trial has had two data cuts, the first in January 2016 (median follow-up 2.9 years from randomisation) and the second in September 2016 ([redacted]). There was little difference, in terms of proportions of patients with events and point estimates, for the two data cuts. Given that the economic model used evidence from the September 2016 data cut only results from that data cut are provided here.

6.6 Details of the trial presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
GALLIUM	BO21223 – A Multicenter, Phase III, Open-Label, Randomized Study in Previously Untreated Patients with Advanced Indolent Non-Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) plus Chemotherapy Compared with Rituximab plus Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders. Report No. 1067980.	September 2016 (31 January 2016 clinical cutoff)
	BO21223 – A Multicenter, Phase III, Open-Label, Randomized Study in Previously Untreated Patients with Advanced Indolent Non-Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) plus Chemotherapy Compared with Rituximab plus Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders. Report No. 1075139.	May 2017 (10 September 2016 clinical cutoff)
	Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: Primary results of the randomized phase 3 GALLIUM study.	Blood. 2016;128(22).
	Pott C, Hoster E, Kehden B, et al. Minimal residual disease in patients with follicular lymphoma treated with obinutuzumab or rituximab as first-line induction immunochemotherapy and maintenance in the phase 3 GALLIUM study.	Blood. 2016;128(22).

Source: Table 2.2.1, p33 of the submission.

6.7 The key features of the GALLIUM trial are summarised in the table below.

Table 3: Key features of the GALLIUM trial

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
GALLIUM	1202	R, OL, Median 41.1 mths	High	Previously untreated advanced follicular lymphoma	PFS, OS	Gain in PFS; QoL; proportion with AEs

AEs=adverse events; OL=open label; mths=months; OS=overall survival; PFS=progression-free survival; QoL=quality of life; R=randomised.
Source: Section 2.3, p34-40; Section 2.4.3, p47-52 of the submission

6.8 The submission stated (p35) that the overall risk of bias in GALLIUM was low. The submission argued that the primary outcome of investigator-assessed PFS was also assessed by an Independent Review Committee (IRC). This however did not remove the potential for bias due to the open-label nature of the trial, particularly given that the primary outcome was investigator-assessed (i.e. unblinded) PFS. In addition, investigator-assessed PFS was used in the economic evaluation. The ESC considered that there was also a high risk of bias in the secondary outcomes of quality of life and reported AEs. Consequently, the PBAC considered the trial to be associated with a high risk of bias.

Comparative effectiveness

6.9 The following table provides a summary of results from the September 2016 data cut for PFS, both investigator-assessed and IRC-assessed, and OS from the GALLIUM trial.

Table 4: Summary of survival outcomes from GALLIUM at the September 2016 data cut - follicular lymphoma population

	G-Chemo (N=601) n/N (%)	R-Chemo (N=601) n/N (%)	Absolute difference	HR (95% CI)
Investigator-assessed PFS September 2016 data cut				
Patients with event	120 (20.0%)	161 (26.8%)	-6.8%	
Median PFS-months (95%CI)	[redacted]	[redacted]	[redacted]	**0.68 (0.54, 0.87)**
IRC-assessed PFS September 2016 data cut				
Patients with event	108 (18.0%)	141 (23.5%)	-5.5%	
Median PFS-months (95%CI)	[redacted]	[redacted]	[redacted]	**0.72 (0.56, 0.93)**
OS September 2016 data cut				
Patients with event	43 (7.2%)	52 (8.7%)	-1.5%	
Median months OS (95% CI)	[redacted]	[redacted]	[redacted]	0.82 (0.54, 1.22)

G-Chemo=obinutuzumab+chemotherapy; HR=hazard ratio (**bold**=statistically significant); IRC=Independent Review Committee; PFS=progression-free survival; OS=overall survival; R-Chemo=rituximab+chemotherapy
Source: Table 2.6.1, p60-61 of the submission

6.10 The results are more favourable for obinutuzumab+chemotherapy for investigator-assessed PFS (showing a 32% decrease in risk of an event) versus IRC-assessed PFS (28% decrease). The PBAC noted the investigator-assessed PFS, which has a greater risk of bias than independently-assessed PFS, was the primary outcome in GALLIUM and also the source of PFS data used in the economic model.

6.11 The Kaplan-Meier plots for investigator-assessed PFS and OS are provided in the figures below.

Figure 1: Investigator-assessed PFS in patients with follicular lymphoma in GALLIUM - September 2016 data cut

Source: Figure 2.6.1, p63 of the submission

Figure 2: OS in patients with follicular lymphoma in GALLIUM - September 2016 data cut

Source: Figure 2.6.3, p66 of the submission

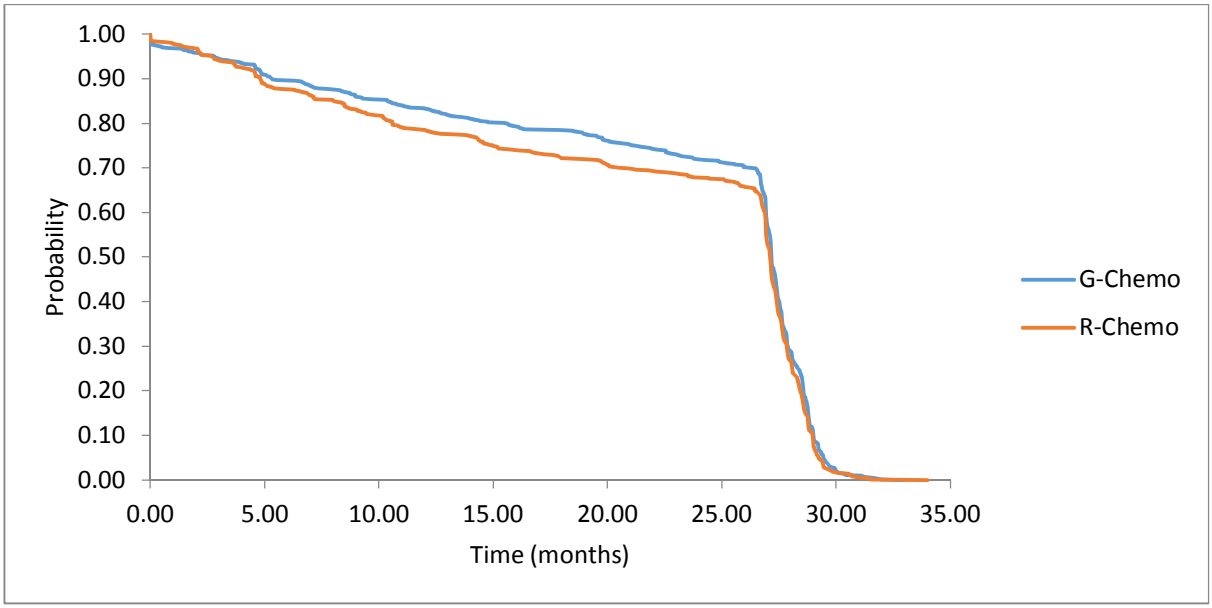
6.12 Median OS was not reached for either obinutuzumab+chemotherapy or rituximab+chemotherapy, less than [redacted]% of patients had died in each arm as of the September 2016 data cut, and there was no statistically significant difference between the two treatment arms. The submission noted (p60) that the hazard ratio for OS was numerically in favour of treatment with obinutuzumab+chemotherapy. While this was the case, the submission based its claim of superiority on PFS results (see 'Clinical claim' below). The PBAC

considered PFS to be a potentially important endpoint in indolent diseases such as follicular lymphoma, even if not all progressions are symptomatic.

6.13 The PBAC noted the results for additional secondary outcomes including time to next anti-lymphoma treatment, event-free survival, and duration of response demonstrated statistically significant advantages for obinutuzumab but considered the results to be modest. The PBAC also noted that there were no statistically significant differences in end of induction treatment response and disease-free survival between the two treatment arms.

6.14 The ESC reviewed the Kaplan-Meier plot for time to treatment discontinuation, and noted that the curve was consistent with the requirement for patients to receive a maximum treatment duration of 2.5 years. The PBAC noted that data pertaining to the ongoing benefit of treatment once patients had received the maximum duration of therapy were limited.

Figure 3: Time to treatment discontinuation in patients with follicular lymphoma in GALLIUM – September 2016 data cut



Source: Excel workbook 'Economic Evaluation.xlsx'

Comparative harms

6.15 The PBAC noted that in general, there were significantly more serious AEs, treatment-related serious AEs and AEs leading to dose modification or interruption in the obinutuzumab+chemotherapy-treated patients than in the rituximab + chemotherapy patients in the GALLIUM trial, particularly in the elderly population (see below). The submission concluded (p75) that despite these differences in AEs there were similar incidences of withdrawal in the two treatment arms and no new safety signals were identified, and thus the side effect profile of obinutuzumab+chemotherapy is clinically manageable. The submission did draw a conclusion of inferior safety with obinutuzumab and has included a number of AEs in its economic model, as presented in the table below.

Table 5: Grade 3-5 AEs with statistically significant differences and AEs of special interest in the follicular lymphoma population (September 2016 data cut)

AE	G-Chemo (N=595) n/N (%)	R-Chemo (N=597) n/N (%)	RR (95% CI)
Grade 3-5 AEs with incidence rate ≥5%			
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]
Serious AEs of special interest - used in economic model			
Serious infusion-related reactions	[redacted]	[redacted]	[redacted]
Serious neutropenia	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]
Serious thrombocytopenia	[redacted]	[redacted]	[redacted]
Serious cardiac events	[redacted]	[redacted]	[redacted]
Serious second malignancies	[redacted]	[redacted]	[redacted]

G-Chemo=obinutuzumab+chemotherapy; R-Chemo=rituximab+chemotherapy; RR=relative risk (**bold**=statistically significant).
Source: Table 2.6.12, p80; Table 2.6.16, p83 of the submission.

6.16 In addition to the AEs discussed in the submission, the draft PI for obinutuzumab includes a special warning for progressive multifocal leukoencephalopathy (PML). This warning states that PML, including fatal PML, can occur in patients receiving obinutuzumab. The submission did not provide any discussion of the occurrence of PML. The CSR indicated that were no cases of PML reported in either treatment arm of GALLIUM (Table 86, p256 of the September 2016 CSR).

6.17 The PBAC noted that the draft product information for obinutuzumab provided with the submission states that patients aged ≥ 65 years of age in the GALLIUM trial experienced more serious AEs and AEs leading to withdrawal or death than patients < 65 years of age. The PBAC were concerned that for elderly patients treated with obinutuzumab+chemotherapy versus those treated with rituximab+chemotherapy, there was an [redacted]% increase in the incidence of serious AEs ([redacted]% versus 50.7% respectively), an [redacted]% increase in AEs leading to withdrawal from any treatment ([redacted]% versus [redacted]% respectively), and a [redacted]% increase in AEs leading to death ([redacted]% versus [redacted]%).

6.18 In its consideration of obinutuzumab for use in rituximab-refractory follicular lymphoma in November 2016, the PBAC recalled that it had indicated that obinutuzumab plus bendamustine followed by obinutuzumab maintenance was of inferior safety to bendamustine monotherapy. However, the PBAC previously noted that obinutuzumab had an overall tolerable safety profile, and that the benefits of its use outweighed its toxicities in the rituximab-refractory setting (paragraph 6.29, November 2016 obinutuzumab PSD).

Benefits and harms

6.19 A summary of the comparative benefits and harms for obinutuzumab+chemotherapy versus rituximab+chemotherapy is presented in the table below.

Table 6: Summary of comparative benefits and harms for obinutuzumab+chemotherapy and rituximab+chemotherapy

Benefits				
Progression-free survival				
GALLIUM	**Obinutuzumab**	**Rituximab**	**Absolute difference**	**HR (95% CI)**
Progressed n(%)	120 (20.0%)	161 (26.8%)	-6.8%	
Median mths PFS	[redacted]	[redacted]	[redacted]	0.68 (0.54, 0.87)
Overall survival				
Died n(%)	43 (7.2%)	52 (8.7%)	-1.5%	
Median mths PFS	[redacted]	[redacted]	[redacted]	0.82 (0.54, 1.22)

Harms						
GALLIUM	**Obi**	**Ritux**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**
				Obi	**Ritux**	
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infusion-related reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious cardiac events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Median duration of follow-up: GALLIUM = 41.1 months
obi=obinutuzumab; RD = risk difference; RR = risk ratio; ritux=rituximab
Source: Table 2.6.1, p60-61; Table 2.6.12, p80; Table 2.6.16, p83 of the submission.

6.20 On the basis of evidence (GALLIUM trial) presented by the submission, for every 100 patients with advanced follicular lymphoma who are treated with obinutuzumab+chemotherapy in comparison to rituximab+chemotherapy, over a median duration of follow-up of 41.1 months:

- Approximately [redacted] more patients would remain progression free, although there is no significant difference in overall survival, which is over 90% in both groups;
- Approximately [redacted] additional patients would experience neutropenia (low white blood cell count, which carries an increased risk of infection);
- Approximately [redacted] additional patients would experience serious infusion-related reactions; and
- Approximately [redacted] additional patients would experience serious cardiac events.

Interpretation of the clinical evidence

6.21 The submission described obinutuzumab in combination with chemotherapy used for induction treatment, followed by obinutuzumab maintenance monotherapy for responders, as superior in effectiveness in terms of PFS and inferior in safety compared with rituximab in combination with chemotherapy as induction treatment, followed by rituximab maintenance monotherapy for responders, in patients with previously untreated advanced follicular lymphoma. The submission did note (p97) that the hazard ratio for OS was numerically in favour of obinutuzumab.

6.22 While the claim of superior effectiveness was adequately supported by the evidence with regard to a statistically significant advantage for obinutuzumab+chemotherapy in PFS (HR=0.68; 95% CI: 0.54, 0.87), the

clinical significance of this claim is uncertain. In the GALLIUM trial response and progression were assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). This paper stated that whether a prolongation of PFS represents direct clinical benefit or is an acceptable surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. While the Pre-Sub-Committee Response (PSCR) (p1) argued that PFS translates into improved quality of life, the PBAC noted that no difference in health-related quality of life measures was observed between obinutuzumab and rituximab in the GALLIUM trial.

6.23 The GALLIUM trial results indicated obinutuzumab to be inferior in safety compared to rituximab. In particular, trial results demonstrated statistically significantly greater occurrence of a range of AEs, including Grade 3-4 neutropenia, serious infusion-related reactions and serious cardiac events. The PBAC noted an [redacted]% increase in the incidence of serious AEs in those aged ≥ 65 years treated with obinutuzumab+chemotherapy versus those treated with rituximab+chemotherapy. The pre-PBAC response (p2) stated that a risk management plan is in place to monitor all identified and potential risks as well as nurse educators across Australia to provide training on safe infusions. The PBAC was concerned that the modest gain in PFS may be offset by the toxicity profile of obinutuzumab.

6.24 The submission also stated (p97) that clinically meaningful and sustained improvements in health-related quality of life were observed in GALLIUM. The submission added that these results suggested that lymphoma-related symptoms were reduced by both treatments and that the resulting improvements in well-being were not nullified by treatment-related side effects and these results supported the relative benefit of obinutuzumab+chemotherapy over rituximab+chemotherapy. The PBAC considered that the quality of life data were potentially biased in this open-label study, and noted that no benefit in quality of life was observed with obinutuzumab compared to rituximab. The submission did not provide any statistical comparisons of the quality of life scales used in the submission (FACT-Lym and EQ-5D).

6.25 The PBAC considered that the applicability of results of GALLIUM trial to PBS population, particularly with respect to risk of toxicity, is not clear. Citing the IPSOS Oncology Monitor (2017) the submission (p92) indicated that Australian patients had a mean age of [redacted] years with [redacted]% reporting at least one co-morbidity, most often cardiovascular. The PBAC noted that the intended PBS population was on average age [redacted] years older than the trial population (mean age 57.9 years). The PBAC considered that given these characteristics, the toxicity would be expected to be higher in the Australian PBS population.

6.26 On the basis of the results provided in GALLIUM, it may not be reasonable to consider that the favourable PFS results represent a direct clinical benefit or an acceptable surrogate for clinical benefit. While the PBAC consideration of

obinutuzumab for treatment of rituximab-refractory follicular lymphoma in November 2016, considered despite limited follow up (24 months and median survival not reached) obinutuzumab was likely to demonstrate an OS benefit with additional follow-up (paragraph 7.5, November 2016 obinutuzumab PSD), it was uncertain whether the same could be concluded from the GALLIUM trial. The GALLIUM trial reported no difference in OS at a median follow up of 41.1 months (less than [redacted]% of patients had died in each arm as of the September 2016 data cut). The PBAC considered the clinical significance of the change in PFS to be uncertain, as no benefit in quality of life was observed with obinutuzumab compared with rituximab. The PBAC noted there was a modest improvement in PFS without a demonstrated survival benefit. The PBAC agreed with the pre-PBAC response (pp2-3) that PFS is a potentially important endpoint in indolent diseases. However, the PBAC reiterated its concern that the modest gain in PFS may be offset by the toxicity profile of obinutuzumab.

6.27 The PBAC considered that the claim of clinically significant superior comparative effectiveness in terms of PFS of obinutuzumab+chemotherapy compared with rituximab+chemotherapy in patients with previously untreated advanced follicular lymphoma was not adequately supported by the data. The PBAC was concerned that the modest gain in PFS over rituximab may be offset by increases in serious AEs. In addition, the PBAC noted that no difference in OS or health-related quality of life measures was demonstrated between treatment arms.

6.28 The PBAC considered that the claim of inferior comparative safety of obinutuzumab+chemotherapy compared with rituximab+chemotherapy was supported by the data.

Economic analysis

6.29 The submission presented a stepped economic evaluation, based on the GALLIUM trial using extrapolation of trial data and employing a five health state Markov model. The type of economic evaluation presented was a cost-utility analysis. A summary of the model structure is provided in Table 7. The PBAC considered the model structure to be appropriate.

Table 7: Summary of the model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis	This was appropriate.
Outcomes	Life years gained (LYG); quality-adjusted life years (QALYs)	This was appropriate.
Time horizon	20 years	AIHW and SEER data were cited by the submission (p107) to support the use of a 20 year time horizon, as well as the July 2015 PBAC submission for bendamustine which used a 20 year model. The 20 year time horizon favoured obinutuzumab (see sensitivity analysis results below) and the submission's justification of the time horizon may not be adequate (see below).
Methods used to generate results	Markov model	This was appropriate.
Health states	5 health states: • PFS on/off treatment • Asymptomatic progression • Symptomatic progression • Subsequent progression • Death	The submission indicated (p105) the selected health states aligned with the treatment algorithm, reflected the disease course and was based on previous model structures accepted by the PBAC. The number and type of health states was appropriate although switching to 3 health states (progression-free, progression, death) had minimal impact on the ICER ($[redacted] decrease; see results below).
Cycle length	1 week with half cycle correction	The submission stated (p108) a half cycle correction was included for completeness. This was reasonable.
Transition probabilities	Sourced from the GALLIUM trial	Progression-free: Kaplan-Meier estimates from GALLIUM until median follow-up of 41.1 months then parametric survival functions were used for the remainder of the 20 year time horizon. PFS to asymptomatic progression: Proportion of patients leaving PFS minus those who directly transition to symptomatic progression or experienced death. PFS to symptomatic progression: Treatment arm specific probability for time to next anti-lymphoma treatment to the proportion of patients leaving PFS minus those who experienced death. Asymptomatic progression to symptomatic progression: Treatment arm specific probability for time to next anti-lymphoma treatment to the proportion of patients remaining in the asymptomatic progression health state minus the patients who experienced death. PFS to death: Patients transitioning out of the PFS health state were assumed to experience death or disease progression. The probability of death for those who remained progression-free was assumed to be the maximum of either age- or gender-specific background mortality observed in the Australian population or the treatment arm-specific mortality rate observed in PFS in GALLIUM. The remainder of patients were assumed to experience disease progression. Progression (asymptomatic and symptomatic) to death: Treatment arm-specific transition probabilities for post-progression survival from GALLIUM. The available extrapolation parameters produced varying results, raising concern about the selection of base case parameters.

AIHW=Australian Institute of Health and Welfare; CLL/SLL=chronic lymphocytic leukaemia/small lymphocytic lymphoma; PFS=progression free survival; SEER=Surveillance, Epidemiology and End Results Program
Source: Table 3.1.2, p101 of the submission.

6.30 The key drivers of the model are identified in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	20 years. The model was sensitive to the time horizon. The submission cited registry data to support high survival rates (eg 72.1% after 5 years). While the survival rates do suggest lengthy survival, it is not likely that the data that was used for these registry estimates closely matches the proposed PBS population. In particular, there was no indication in the submission that the survival rates sourced from AIHW and SEER are based on treated patients only or on all patients with NHL or follicular lymphoma (the AIHW rates are based on patients at diagnosis). It is reasonable to assume the data sources are referring to all patients and not just treated patients, as it is likely such would be specified. Consequently, the cited survival rates cannot be assumed to reflect those of the proposed PBS population. The ESC agreed with the evaluators that the survival rates sourced from AIHW and SEER may not be directly applicable to the proposed PBS population.	High, favoured obinutuzumab
Extrapolation	Log-normal extrapolation of PFS after a median 41.1 months follow-up. As illustrated by Figure 5, length of time in PFS and differences between treatment arms varied greatly depending on the extrapolation function used.	High, favoured obinutuzumab
Assumed survival benefit due to delay in progression	While there was no statistically significant difference in OS, the model assumed a survival benefit for obinutuzumab-treated patients. A large portion of this assumed benefit was generated by delayed disease progression.	High, favoured obinutuzumab
Treatment specific death rates applied post-progression and in PFS	The submission assumed a lower death rate for obinutuzumab compared with rituximab-treated patients in the progression health states. Death was also assumed to occur in the PFS health state, the probability was similar between obinutuzumab and rituximab but was slightly higher for the obinutuzumab arm (as was observed in the trial).	High, favoured obinutuzumab

Source: Table D.2, p14 of Section D of the submission

6.31 As part of the 9 steps of the stepped economic evaluation, the submission included the effective price of obinutuzumab as step 9, and the published price was used in the preceding 8 steps. The submission's presentation of costs in steps 1 to 8 based on the published price of obinutuzumab, with the effective price of obinutuzumab added in step 9 was not informative for assessment of each step of the modelled evaluation as it inflated the ICERs by close to [redacted] times their value based on the effective price. Consequently, the results provided in the table below use the effective price of obinutuzumab from step 1. In addition, current dispensing fees and preparation fees were added to the obinutuzumab and rituximab costs; given these factors the results provided in Table 9 below differ from those in the submission.

6.32 While utility values were added in step 5 of the modelled evaluation, the submission indicated (p127) that the weighting of life years to determine QALYs automatically occurs inherently at each step of the model. As such, results for incremental cost/QALY at each step of the model were provided in the submission and are therefore also provided in the table below. However,

since the results for step 5 when utility values are added are the same as the results for the previous step, the step 5 results have not been included in the table below. The ESC noted the submission sourced utility values from GALLIUM via EQ-5D scores and also applied literature-derived utility values. The ESC considered this approach to be appropriate.

Table 9: Results of the stepped economic evaluation[a]

Step and component	G-Chemo	R-Chemo	Increment
Step 1: trial-based costs and outcomes (60.1 and 58.4 months of data)			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG gained			**$**
Incremental cost/QALY			**$**
Step 2: modelled evaluation across 20 years			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$**
Incremental cost/QALY			**$**
Step 3: incorporation of medical resource use costs			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$**
Incremental cost/QALY			**$**
Step 4: incorporation of AE costs			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$**
Incremental cost/QALY			**$**
Step 5: incorporation of utility values (incorporated at each step in this table)			
Step 6: Inclusion of post-progression therapy			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$**
Incremental cost/QALY			**$**
Step 7: Inclusion of end of life costs			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$** *
Incremental cost/QALY			**$** *
Step 8: Convergence of survival curves			
Costs	$	$	$
LYG			
QALY			
Incremental cost/LYG			**$**
Incremental cost/QALY			**$**
Step 9: Inclusion of effective price for obinutuzumab – results are the same as for step 8 as effective prices used in all of the above steps			

[a] Drug prices were updated during the evaluation to include dispensing fees and preparation fees as of 1 July 2017. Given these alterations, all estimated costs differ slightly from those presented in the submission.

* Values were corrected by the sponsor in the PSCR.

G-Chemo=obinutuzumab+chemotherapy; LYG=life years gained; QALY=quality adjusted life year; R-Chemo=rituximab+chemotherapy

Source: Tables 3.8.1 to 3.8.7, p125-128 of the submission; Excel workbook 'Economic Evaluation.xlsx'

6.33 As would be anticipated, there was a considerable drop between the trial-based step 1 result (cost/LYG=$105,000 - $200,000) and the modelled evaluation (step 2: cost/LYG=$15,000 - $45,000; cost/QALY=$15,000 - $45,000). There was little change in the ICER with addition of AE costs while

inclusion of costs of post-progression therapy and end of life costs reduced the ICER by about $[redacted]. The ICER returned to levels similar to that seen in step 2 of the model (cost/QALY=$15,000 - $45,000) with inclusion of the convergence of survival curves $15,000/QALY - $45,000/QALY). The submission stated (p114) that convergence was applied to both PFS and OS. The PBAC noted that while PFS did converge over the model time horizon (20 years in the base case), OS did not converge within the model time horizon. This is demonstrated in the figure below. Examination of the Excel workbook indicated that convergence was not applied to OS.

Figure 4: Overall survival and progression free survival curves (base case: 20 year time horizon)

[redacted]

Source: Figure 3A.4.3, p114 of the submission

6.34 The ESC noted that the submission assumed that patients treated with obinutuzumab+chemotherapy would continue to benefit from treatment over the 20 year time horizon in the economic model, despite the maximum treatment duration of 2.5 years of obinutuzumab+chemotherapy in the GALLIUM trial. The ESC noted that while continued benefit was assumed beyond the trial duration, no treatment costs occurred beyond 2.5 years. The PBAC considered this may be an overestimate of the duration of benefit derived from treatment and hence the ICER may be underestimated.

6.35 The results of the stepped economic evaluation indicated that the key components of the model were the chosen time horizon and underlying extrapolated data.

6.36 The submission also provided results for a 3 health state model (PFS, progression, death). These results are provided in the table below with the submission base case (5 health states) included for reference.

Table 10: Results of 3 health state model[a]

Component	G-Chemo	R-Chemo	Increment
3 health states			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/LYG			**$** [redacted]
Incremental cost/QALY			**$** [redacted]
Submission base case (5 health states) for reference			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/LYG			**$** [redacted]
Incremental cost/QALY			**$** [redacted]

[a] Drug prices were updated during the evaluation to include dispensing fees and preparation fees as of 1 July 2017. Given these alterations, all estimated costs differ slightly from those presented in the submission.

G-Chemo=obinutuzumab+chemotherapy; LYG=life years gained; QALY=quality adjusted life year; R-Chemo=rituximab+chemotherapy

Source: Table 3.8.3, p126 of the submission; Excel workbook 'Economic Evaluation.xlsx' provided with the submission.

6.37 There was only a $[redacted] difference between the 3 health state and 5 health state models for incremental cost/QALY. While the PBAC had indicated the need for a health state to account for patients who are progressed but well (paragraph 7.13, July 2014 obinutuzumab PSD), the inclusion of two additional health states to account for this in the current model appeared to have little impact.

6.38 The ESC reviewed the sensitivity analysis around utility weights applied in the economic model presented in the submission (p131) and noted that varying the choice of utilities had minimal impact on the ICER. The PBAC considered this indicates the QALY gains in the model are driven by OS outcomes, which were not statistically significant in the GALLIUM trial. The PBAC did not consider it appropriate for the economic model to be driven by immature OS data.

6.39 Sensitivity analyses demonstrated that the model was sensitive to the chosen time horizon and the method of PFS extrapolation used (Table 11). For example, decreasing the time horizon from the submission's base case of 20 years to 15 years increased the ICER by almost [redacted]%, to $15,000/QALY - $45,000/QALY. A 10 year time horizon increased the ICER to $75,000/QALY - $105,000/QALY. The pre-PBAC response (p3) argued that PBAC accepted a 20 year time horizon at its July 2015 consideration of bendamustine for indolent NHL. The PBAC noted that in this submission the OS did not converge within the model time horizon and considered it was uncertain that the assumed survival difference favouring obinutuzumab would be realised. The PBAC recommended a shorter time horizon would be more appropriate.

Table 11 Results of sensitivity analyses

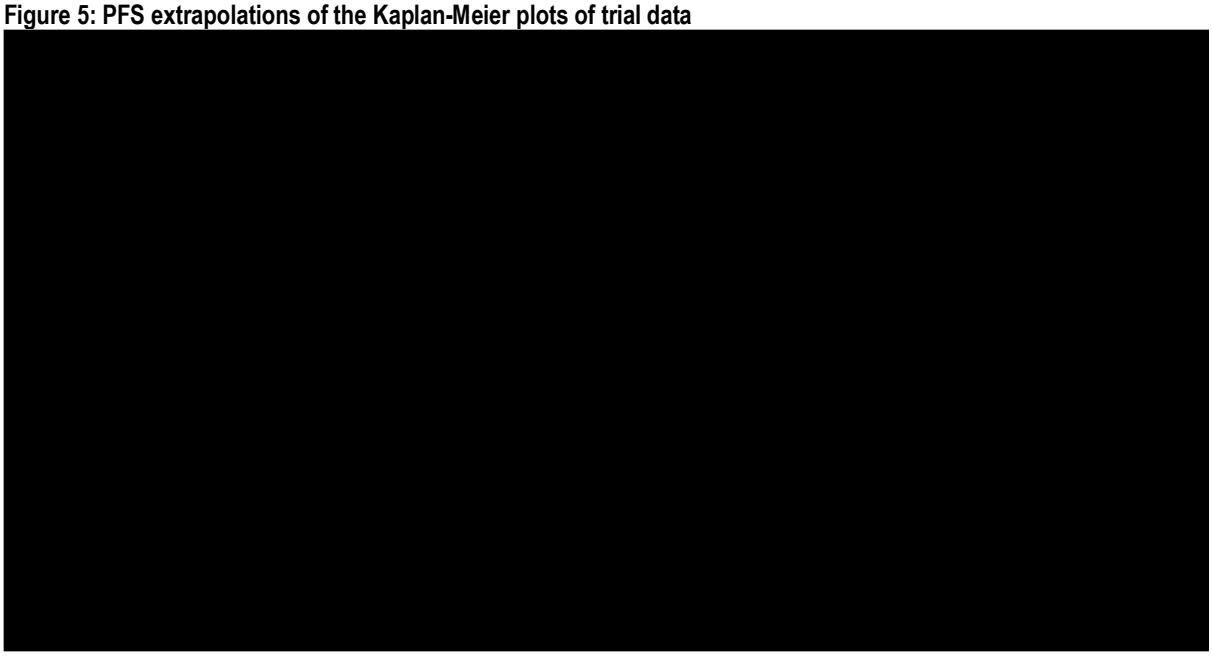
Analyses	Incremental cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]
Discount rate (base case: 5% costs and outcomes) 0% costs and outcomes 3.5% costs and outcomes	[redacted]	[redacted]	[redacted]
Time horizon (base case: 20 years) 15 years 25 years 10 years 5 years	[redacted]	[redacted]	[redacted]
Extrapolation (base case: KM to 41.1 months and log-normal extrapolation) Parametric extrapolation when 90% of events occurred ([redacted] months) KM to 41.1 months and Weibull extrapolation Weibull extrapolation KM to 41.1 months and exponential extrapolation KM to 41.1 months and log-logistic extrapolation KM to 41.1 months and gamma extrapolation KM to 41.1 months and Gompertz extrapolation Gompertz extrapolation Overall survival (risk of progression death) equal between obi and ritux (obi risk) Overall survival (risk of progression death) equal between obi and ritux (ritux risk)	[redacted]	[redacted]	[redacted]
Multivariate analyses			
15 year time horizon + KM to 41.1 months with Weibull extrapolation 10 year time horizon + KM to 41.1 months with Weibull extrapolation 15 year time horizon + KM to 41.1 months with gamma extrapolation 10 year time horizon + KM to 41.1 months with gamma extrapolation 15 year time horizon + KM to 41.1 months with Weibull extrapolation + equal risk progression death (obi) 15 year time horizon + KM to 41.1 months with Weibull extrapolation + equal risk progression death (ritux) KM to 41.1 months with Weibull extrapolation + equal risk progression death (obi) KM to 41.1 months with Weibull extrapolation + equal risk progression death (ritux)	[redacted]	[redacted]	[redacted]

Source: Table 3.9.1, p130; Table 3.9.2, p131 of the submission and Excel workbook 'Economic Evaluation.xlsx'.

6.40 The model was sensitive to the extrapolation function used, and alternate PFS extrapolation methods (submission used log-normal beyond median follow up for the base case) produced varying results, with ICERs ranging from $15,000/QALY - $45,000/QALY to over $45,000/QALY - $75,000/QALY (base case $15,000/QALY - $45,000/QALY). Much of the variability was due to uncertain fit of the parametric functions beyond trial data (shape of the tail distributions). The ESC noted that there were minimal differences in Akaike Information Criteria (AIC) values between log-normal, Weibull, gamma and log-logistic extrapolation functions. The ESC noted the Kaplan-Meier plots with the extrapolated log-normal plots and an alternative plot using the Weibull function (Figure 5). The ESC agreed with the evaluator that while

both Weibull and log-normal curves appear to follow the Kaplan-Meier trial-based curves, their extrapolated data varied greatly with the log-normal function allowing patients to spend a far greater time in PFS. The PSCR (p3) argued that the log-normal extrapolation applied in the economic model was the most objective based on statistical criteria and confers the greatest level of fit visually. The PSCR (p3) also argued the log-normal extrapolation appropriately predicts what is clinically reasonable and plausible based on Australian survival data in lymphoma sourced from AIHW. Additionally, the pre-PBAC response (p3) argued that the commentary applied extrapolations resulting in implausible outcomes, contrary to Australian observed data that shows 51.3% of NHL patients alive after 20 years. The PBAC noted the alternate extrapolation methods for PFS produced varying results. Changing log-normal to Weibull extrapolation for both treatment arms increased the ICER to $15,000/QALY - $45,000/QALY while applying gamma extrapolation decreased the ICER by less than $[redacted] to $15,000/QALY - $45,000/QALY.

Figure 5: PFS extrapolations of the Kaplan-Meier plots of trial data



6.41 The modelled benefit with obinutuzumab was driven by the difference in PFS, and related to this the Commentary requested that the results of the economic model be provided using IRC-assessed PFS instead of investigator-assessed PFS. This was not provided in the PSCR, rather it was noted that the PFS results were similar for PFS assessed by IRC (HR 0.72; 95% CI 0.56, 0.93) and investigators (HR 0.68; 95% CI 0.54, 0.87). The PBAC noted relatively small changes in the PFS results may impact on the ICER given this outcome drives the model and is extrapolated over a long time period. The PBAC considered that extrapolation using PFS assessed by the IRC would be informative.

6.42 The PBAC noted the model was also sensitive to the application of treatment specific death rates within each health state (Table 11). When the risk of progression death and dying in PFS was made equal between obinutuzumab and rituximab, the ICER increased to $15,000/QALY - $45,000/QALY

(obinutuzumab probability) and to $15,000/QALY - $45,000/QALY (rituximab probability). The PBAC noted that this scenario maintains the advantage in survival due to delayed disease progression and the immature OS data do not allow this to be fully tested.

6.43 Combining shortening of the time horizon (to 15 years), use of Weibull extrapolation (beyond median follow up of 41.1 months) and removing the difference in the additional risk of death for progressed patients and patients in PFS (but not the inherent OS benefit associated with delayed progression) resulted in an ICER of $75,000/QALY - $105,000/QALY when the risk of death was the rituximab risk for both arms; and $75,000/QALY - $105,000/QALY when the obinutuzumab risk was applied to both arms (Table 11). While the time horizon had impacted on many of the analyses presented, altering extrapolation (Weibull post Kaplan Meier) and equalising the additional risk of death applied in the PFS and post-progression states, but leaving the time horizon at 20 years resulted in ICERs of around $75,000/QALY - $105,000/QALY, therefore demonstrating the independent importance of PFS extrapolation and death to the modelled results. The PSCR (p3) claimed that the multivariate analyses unreasonably focus on combining issues that had been addressed independently (i.e. model time horizon, extrapolation and survival benefit) and result in implausible survival outcomes. The pre-PBAC response (p3) presented counter-factual multivariate sensitivity analysis assuming a time horizon of 25 years and a log-logistic extrapolation which resulted in an ICER of $15,000/QALY - $45,000/QALY. The PBAC considered the analyses testing the key model assumptions informative.

6.44 The PBAC considered the ICER was highly uncertain because it was driven by the gain in OS which was non-significant in the trial and relied on extensive extrapolation.

Drug cost/patient/year: $[redacted]

6.45 The estimated cost for a year of treatment with obinutuzumab was $[redacted] (updated for current dispensing and preparation fees). This was based on nine cycles of treatment (11 vials) which included a full induction course (6 cycles of therapy) as well as three cycles of obinutuzumab maintenance. The PBAC noted that induction therapy for obinutuzumab varies between 8 to 10 doses and the submission selected the lower of those, 8 doses, to determine cost. The PBAC considered the dosing regimen for obinutuzumab in the GALLIUM trial may include a higher number of doses per induction cycle than required in clinical practice.

6.46 The submission did not provide corresponding 1 year costs for patients treated with rituximab. This cost was calculated during the evaluation using the same methodology as the submission applied for obinutuzumab costs. The estimated cost for a year of treatment with rituximab was $[redacted] (updated for current dispensing and preparation fees and pharmacy mark-up). As for obinutuzumab, this was based on nine cycles of treatment that included a full induction course (6 cycles of therapy) as well as three cycles of

rituximab maintenance. For induction with rituximab, 6 to 8 doses are recommended. Consistent with the submission's approach for obinutuzumab, the lower end of the range was used for the rituximab costing. The same weighted price per administration (32% public hospital; 68% private hospital) was applied.

6.47 The PBAC considered the drug cost of obinutuzumab to be significantly higher than rituximab. The PBAC noted the difference in drug cost to the PBS based on the proposed treatment course is further magnified when treatment is combined with bendamustine, as obinutuzumab maintenance after bendamustine-obinutuzumab induction is proposed to replace the current standard of no maintenance after bendamustine-rituximab induction.

Estimated PBS usage & financial implications

6.48 This submission was not considered by DUSC. The submission employed an epidemiological approach to develop the financial estimates. AIHW data was used to estimate the follicular lymphoma population and market research was used to estimate the uptake rate. The proportion of patients achieving a response and moving on to maintenance treatment was based on the GALLIUM trial, as were the dosages used. It was assumed that obinutuzumab would substitute for rituximab. The PBAC considered that the uptake rate proposed may be underestimated.

6.49 The table below provides a summary of estimated patient numbers, scripts and costs to PBS and the Government.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated - induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion going on to maintenance treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated - maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts - induction and maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications						
Overall net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to government for MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Drug prices were updated during the evaluation to include dispensing fees and preparation fees as of 1 July 2017. Given these alterations, all estimated costs differ slightly from those presented in the submission.

Source: Tables 4.2.2 to 4.2.7, p143-46 of the submission and Excel workbook 'Section 4 Workbook'.xlsx.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $10 - $20 million per year.

6.50 Estimated net costs to the Government over the first 6 years of listing were $60 - $100 million. The PBAC considered that it is not likely that the uptake rate [redacted] across the first 6 years of listing, and it is also possible that treatment response and dosage (based on GALLIUM) may not be reflected in clinical practice. The PBAC considered that the uptake rate proposed may be underestimated. As such, the degree of certainty regarding the estimates is difficult to determine.

Financial management – risk sharing arrangements

6.51 The submission proposed a subsidisation cap, that it stated (p166) represents the proportion of expected utilisation for obinutuzumab within the total population with previously untreated follicular lymphoma who are eligible for obinutuzumab. The following table provides the proposed subsidisation caps for obinutuzumab. The caps were based on a [redacted]% uptake rate. The sponsor proposed that any expenditure above this subsidisation cap would trigger a rebate by the sponsor to Government, [redacted]. The submission added that since obinutuzumab is the first submission of a new molecule in class based on a cost-effectiveness analysis with rituximab in this population, it is reasonable that any additional new molecules for the previously untreated advanced follicular lymphoma would require a [redacted] prior to PBS listing. The PBAC considered the subsidisation cap proposed in the submission may not be reasonable, given there were uncertainties with the uptake rates proposed.

Table 13: Proposed subsidisation caps for obinutuzumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number receiving obinutuzumab (induction and maintenance)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsidisation cap[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The estimated subsidisation caps were updated during the evaluation to include dispensing fees and preparation fees as of 1 July 2017. Given these alterations, all estimated costs differ slightly from those presented in the submission.
Source: Table 4.6.5, p166 of the submission

6.52 Rituximab has a weighted price across several indications. The submission used an AEMP per mg of $3.73 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 (PSD, July 2017, Item 4.04 rituximab).

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of obinutuzumab on the PBS for treatment of previously untreated advanced follicular lymphoma (stage II bulky or stage III/IV), as the clinical need for the majority of patients was already met, and the clinical benefits of therapy over rituximab were uncertain, with no demonstrated improvement in quality of life or OS and an inferior comparative safety profile. Further, the PBAC considered the cost-

effectiveness against rituximab to be 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.

7.2 The PBAC noted that 57% of patients in the GALLIUM trial received bendamustine, and that 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 notes uncertainty regarding the clinical place of obinutuzumab-bendamustine combination followed by obinutuzumab maintenance in this population.

7.3 The PBAC considered 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.

7.4 The PBAC considered that rituximab in combination with chemotherapy for induction treatment and rituximab monotherapy for maintenance treatment as the main comparator was appropriate.

7.5 The PBAC considered the key clinical trial (GALLIUM) to be associated with a high risk of bias due to the open-label nature of the trial, particularly given that the primary outcome was investigator-assessed PFS. The PBAC also considered that there was a high risk of bias in the secondary outcomes of quality of life and reported AEs.

7.6 The PBAC noted that the clinical claim for obinutuzumab over rituximab was made based on superior investigator-assessed PFS. The PBAC reiterated that it considered PFS to be a potentially important outcome in indolent diseases such as follicular lymphoma. However, for this submission the PBAC was concerned that the modest gain in PFS over rituximab may be offset by increases in serious AEs. In addition, the PBAC noted that no difference in OS or health-related quality of life measures was demonstrated between treatment arms. Hence, the PBAC considered the clinical claim of superior effectiveness to be inadequately supported.

7.7 The PBAC considered that the OS data from the GALLIUM trial were immature, with less than [redacted]% of patients in each arm having died as of the September 2016 data cut. The PBAC considered that the absence of a statistically significant OS benefit (HR=0.82; 95% CI: 0.54, 1.22) in the available immature data limits any extrapolations based on these results. The PBAC noted that the OS benefit of obinutuzumab was more favourable in CLL (HR=0.70; 95% CI: 0.47 to 1.02) (paragraph 6.10, March 2015 obinutuzumab PSD).

7.8 The PBAC considered that the claim of inferior safety compared with the rituximab treatment arm was consistent with the data. The PBAC noted with

obinutuzumab+chemotherapy there were statistically significantly more serious AEs and treatment-related serious AEs such as serious infusion-related reactions and serious cardiac events. The PBAC were concerned that the incidence of serious AEs was [redacted]% 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.

7.9 The PBAC was concerned regarding the applicability of the GALLIUM trial results to the intended Australian population. The PBAC noted data indicating the proposed PBS population (mean age [redacted] years) was on average [redacted] years older than the trial population, with [redacted]% reporting at least one co-morbidity. The PBAC considered that given these characteristics, the toxicity of obinutuzumab would be expected to be higher in the Australian PBS population, and the benefits as demonstrated in trial are unlikely to be realised.

7.10 The PBAC noted that the economic model comparing obinutuzumab and rituximab included five health states, and considered this appropriately captured the different treatment phases. The PBAC noted that the QALY gains in the model were driven by the gain in OS, and considered that this did not accurately reflect the available data where there was a difference in PFS but the OS data were immature and the difference was not statistically significant.

7.11 The PBAC noted a 20-year time horizon was used in the submission base case. The PBAC recalled its acceptance of a 20-year time horizon at its July 2015 consideration of bendamustine for indolent NHL, but considered a shorter time horizon of no more than 10 years would be appropriate in this submission for the following reasons. The PBAC noted that there was no significant difference in OS in the trial, and that in the economic model the OS did not converge within the model time horizon. The PBAC considered it was uncertain if the assumed survival benefit favouring obinutuzumab would be realised. In addition, the PBAC noted the model was highly sensitive to the time horizon.

7.12 The PBAC noted the model was sensitive to the extrapolation function used with alternate PFS extrapolation methods producing varying results. The PBAC noted that much of the variability was due to uncertain fit of the parametric functions beyond trial data. The PBAC considered that the log-normal function used in the model favoured obinutuzumab as it allowed patients to spend a far greater time in PFS than other extrapolation methods.

7.13 The PBAC noted the model generated a survival benefit by delaying disease progression as well as by assuming a lower death rate for obinutuzumab compared with rituximab for patients in the post-progression health state. The PBAC considered the difference in death rates post-progression further increased the uncertainty associated with the modelled OS gain.

7.14 The PBAC noted the variability in the ICERs generated within the sensitivity analyses. The PBAC considered that this variability, along with concerns regarding the model time horizon, the PFS extrapolation method, and the assumed survival benefit, indicated that the base case ICER was highly uncertain and likely underestimated.

7.15 The PBAC considered the financial impact of obinutuzumab was uncertain. The PBAC considered that the uptake rate proposed may be underestimated, and noted the high incremental drug cost of obinutuzumab over rituximab.

7.16 The PBAC proposed that any resubmission should be a major submission. The resubmission would need to more clearly establish the clinical need, and demonstrate the clinical benefits, of obinutuzumab over rituximab in the first-line setting. In particular, the Committee would welcome updated data for OS. The PBAC considered that such a submission should revise the economic model to include more conservative assumptions regarding PFS (and hence OS), assume the same death rate for obinutuzumab and rituximab post-progression, use a time horizon of no more than 10 years, and ensure the convergence of survival curves within the modelled timeframe. The PBAC noted that the clinical need for obinutuzumab as a first-line treatment may be restricted to a subgroup of patients only, that had not been identified in the submission.

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

Outcome:

Rejected

8 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.

9 Sponsor's Comment

There remains an unmet need for a novel treatment alternative to rituximab that can prolong progression free survival for all previously untreated patients with advanced stage follicular lymphoma. Roche is committed to working with the Department of Health and the PBAC to enable access to obinutuzumab for people with advanced follicular lymphoma.