Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Polatuzumab vedotin

Proprietary Product Name: Polivy

Sponsor: Roche Products Pty Ltd

December 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the curve
BG	Bendamustine and obinutuzumab
BR	Bendamustine plus rituximab
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMI	Consumer Medicines Information
CR	Complete response
CYP	Cytochrome P40 (enzyme)
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
HR	Hazard ratio
HSCT	Haemopoietic stem cell transplantation
IgG1	Immunoglobulin G1
IV	Intravenous
MDS	Myelodysplastic syndrome
MMAE	Monomethyl auristatin E

Abbreviation	Meaning
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetic(s)
PR	Partial response
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
RMP	Risk management plan
SCT	Stem cell transplant
TGA	Therapeutic Goods Administration
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	18 October 2019
Date of entry onto ARTG:	21 October 2019
ARTG number:	314866
, *Black Triangle Scheme*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Polatuzumab vedotin
Product name:	Polivy
Sponsor's name and address:	Roche Products Pty Limited 30-34 Hickson Road, Sydney NSW 2000
Dose form:	Powder for injection
Strength:	140 mg/mL
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.*
Route of administration:	Intravenous infusion (IV)
Dosage:	The recommended dose of Polivy is 1.8 mg/kg given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. For further information refer to the Product Information (PI).

Product background

This AusPAR describes the application by the sponsor, Roche Products Pty Ltd, to register the new biological entity polatuzumab vedotin as Polivy for the following indications:

> *Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.*

Polivy is proposed to be used in combination with bendamustine and rituximab at a proposed dose of 1.8 mg/kg administered as an intravenous (IV) infusion (over 90 minutes (initial dose) or 30 minutes (subsequent doses)) every 21 days in combination with bendamustine and rituximab for 6 cycles (recommended duration of treatment).

Polatuzumab vedotin consist of a CD79b-targeted antibody-drug conjugate that preferentially delivers a cytotoxic agent, an anti-mitotic agent (monomethyl auristatin E, (MMAE)), to B-cells, which results in the killing of malignant B-cells. Hence, it is intended to allow target specific cytotoxic treatment of malignant B-cells in diffuse large B-cell lymphoma (DLBCL).

DLBCL is a usually treated initially with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), which is curative in approximately 60% of patients. In those who are refractory to first-line therapy, autologous stem cell transplantation (ASCT) is considered. However, given that the average age of onset for DLBCL is 60 to 70 years of age, ASCT is not always possible. In refractory patients in whom ASCT is not an option, there are limited treatment options, and Polivy is intended for use in this group.

Relapsed/refractory DLBCL is a rare condition as it represents only a fraction of patients with DLBCL, itself an uncommon disease. Therefore, the efficacy and safety of Polivy was supported in this submission largely by a single Phase II study.

Regulatory status

This is an application to register a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been submitted in the United States of America (USA) and the European Union (EU) (see Table 1).

Table 1: International regulatory status of Polivy

Country /region	Submission date	Approved indication
USA	19 December 2018	*Polivy in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.* *Accelerated approval was granted for this indication based on complete response rate [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*
EU	20 December 2018	*Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this Priority application and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline for Submission PM-2019-00471-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	15 April 2019
Evaluation completed	17 September 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	26 September 2019
Sponsor's pre-Advisory Committee response	N/A
Advisory Committee meeting	N/A
Registration decision (Outcome)	18 October 2019
Completion of administrative activities and registration on ARTG	21 October 2019
Number of working days from submission dossier acceptance to registration decision*	130

*The statutory time frame is 255 working days. Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

III. Submission overview and risk/benefit assessment

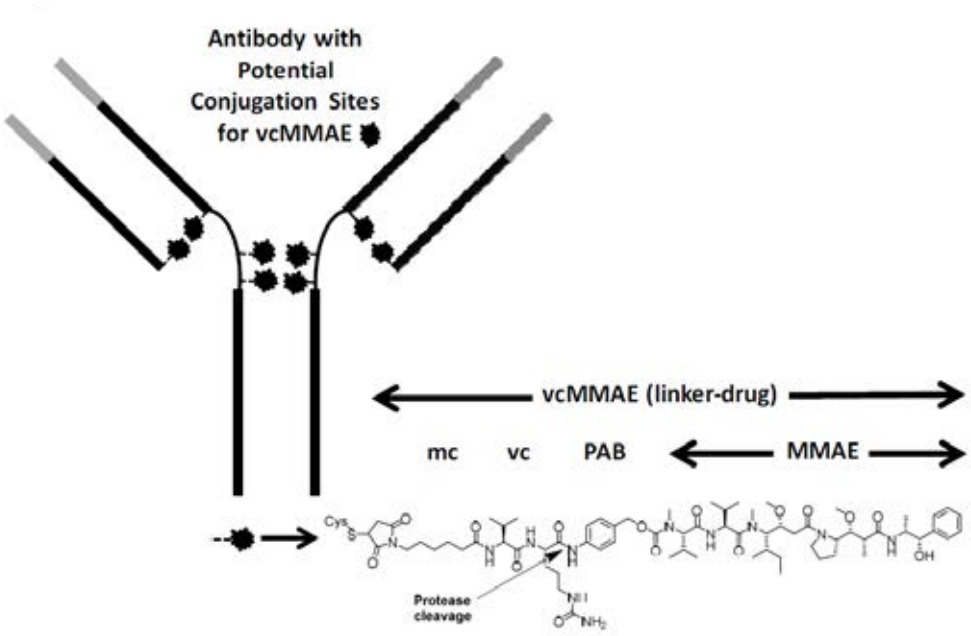
The submission was summarised in the following Delegate's overview and recommendations.

Quality

The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanised immunoglobulin G1 (IgG1) monoclonal antibody via a cleavable linker.

The structure of polatuzumab vedotin is shown in Figure 1 below.

Figure 1: Primary structure of polatuzumab vedotin



The sponsor provided results of characterisation testing, including physicochemical, biological, and immunochemical properties of polatuzumab vedotin.

All drug substance and drug product materials undergo in process control testing and in process acceptance criteria testing. All manufacturing steps and analytical procedures are validated. There are no issues pertaining to manufacture or manufacturer of the product or specifications.

There are no objections to the registration of this product from sterility; endotoxin, viral safety and container safety aspects.

The main issue that the quality evaluation has raised is that the maximum shelf life recommended is 12 months at 2 to 8 °C. This is shorter than originally proposed by the sponsor.

Nonclinical

Primary pharmacology

Mechanism of action

Polatuzumab vedotin is an anti-CD79b antibody conjugated via a protease-cleavable linker (composed of maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl) to the anti-microtubule agent, MMAE. The molar ratio of MMAE to antibody is on average 3.5. CD79b is a B-cell receptor–associated protein and is located on the surface of B-cells. The expression of CD79b is restricted to pre-B-cells and mature B-cells (except plasma cells). It is expressed in a majority of the B-cell derived malignancies, including DLBCL and chronic lymphocytic leukaemia (CLL). Following binding to CD79b expressing cells, polatuzumab vedotin is intended to be internalised and transported to lysosomes, where the MMAE component is released and binds to tubulin, leading to cell cycle arrest and apoptosis.

Toxicology

The nonclinical toxicity of polatuzumab vedotin was assessed in rats and cynomolgus monkey. The nonclinical toxicity of a surrogate antibody-drug conjugate (ADC) (which binds to cynomolgus monkey CD79b) was assessed in cynomolgus monkeys.

The nonclinical evaluator concluded that the studies support the proposed indication for Polivy; specifically:

- The pharmacology studies support the proposed indication for polatuzumab vedotin, that is, to be used in combination with rituximab and bendamustine to treat patients with diffuse B-cell lymphoma. The studies also support the proposed clinical dose.
- Inhibitors/inducers of cytochrome P450 (CYP) isozyme 3A4 or P-glycoprotein are likely to alter the plasma kinetics of MMAE, thereby affecting the safety and efficacy profile of the drug.
- The toxicity findings with polatuzumab vedotin can be attributed to MMAE and are typical for those seen with tubulin-acting agents. Notable findings of clinical relevance in the toxicity studies include:
  - reversible myelotoxicity with secondary haematological effects (both anaemia and leukopaenia) associated with MMAE toxicity and suppression of B-cells associated with the pharmacological activity, indicating a risk for opportunistic infections;
  - gastrointestinal disturbances (vomiting and nausea);
  - reduced male fertility and effects on the testes, which was not completely reversible after a 6 week treatment-free period in rats;
  - reversible hepatotoxicity, which should be easily monitored; and
  - embryofetal lethality and fetotoxicity.
- Given the effects on the testes, the aneugenic properties of MMAE and the adverse embryofetal effects, together with the long half-life of polatuzumab vedotin, a washout period of at least 6 months would be recommended before patients consider becoming pregnant.
- The nonclinical evaluator recommended that the draft PI be amended to specify the embryo-toxicity and limit use in pregnancy.

There are no objections on nonclinical grounds to the registration of polatuzumab vedotin for the proposed indication. Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

Clinical

Pharmacology

The pharmacokinetics of Polivy are consistent with a monoclonal antibody; small volume of distribution with tissue binding mediated by receptor affinity, long half-life and 100% (parenteral) bioavailability.

The main immunogenicity finding is that 2.6% of 536 subjects developed anti-drug antibodies (ADA). This did not appear to be associated with pharmacokinetic effects.

The submitted data did not determine the incidence of neutralising antibodies.

Dose finding for the pivotal study was based on the Phase I Study DCS4968g. The US Food and Drug Administration (FDA) reduced the planned dose of 2.4 mg to 1.8 mg due to toxicity. The clinical evaluator has noted that the nature of this toxicity has not been

specified in the submission. The clinical evaluator has concluded that the choice of the 1.8 mg dose is acceptable.

Efficacy

Efficacy was based on a Phase I/II trial, Study G029365. This compared the efficacy of Polivy + bendamustine + rituximab (Pola + BR) with bendamustine + rituximab (BR) in 80 patients randomised 1:1 to either treatment arm. There were additional treatment arms in the trial not relevant to the proposed indication for which efficacy data was not provided (however safety data was provided).

Enrolled patients had received at least 1 prior treatment for DLBCL and had either relapsed or become refractory as defined by:

- patients who were ineligible for second-line stem cell transplant (SCT), with progressive disease or no response (stable disease) < 6 months from start of initial therapy (2L refractory);
- patients who were ineligible for second-line SCT, with disease relapse after initial response ³ 6 months from start of initial therapy (2L relapsed);
- patients who were ineligible for third-line (or beyond) SCT, with progressive disease or no response (stable disease) < 6 months from start of prior therapy (3L+ refractory); and
- patients who were ineligible for third-line (or beyond) SCT with disease relapse after initial response ³ 6 months from start of prior therapy (3L+ relapsed).

If a patient had received previous bendamustine, they must have had a response of > 1 year to be included.

The clinical evaluator has noted that there was an imbalance in prognostic indicators among patients in the two treatment arms. The BR arm enrolled more patients with high-risk prognosis than did the Pola + BR arm (42.5 versus 22.5% respectively).

The primary endpoint of the study was the rate of complete response (CR) in the two comparator arms.

Table 3: Comparative complete response rates in Pola + BR and BR treated patients in the pivotal trial (Study G029365)

Study Phase	Randomized Phase	
Treatment	**BR Phase II**	**Pola+BR Phase II**
Sample size	**n=40**	**n=40**
Primary Efficacy Endpoint		
CR at PRA by PET (IRC assessed)		
n (%)	7 (17.5%)	16 (40.0%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(24.9, 56.7)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	22.5 (2.6, 40.2); p=0.0261	

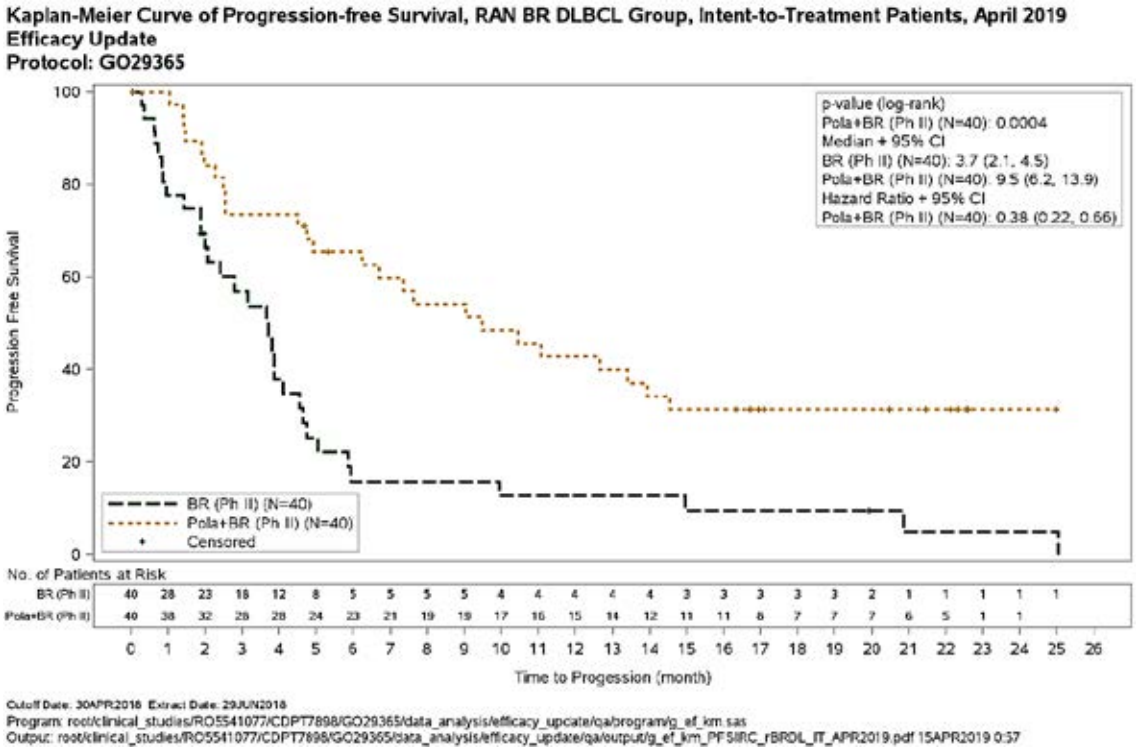
PET = positron emission tomography; CI = confidence interval; PRA = primary response assessment; IRC = independent review committee.

The CR response rate was 40% in the Pola + BR group and 17.5% in the BR group, a difference of 22.5% (95% confidence interval (CI): 2.6 to 40.2%).

Secondary endpoints

Overall 70% of patients in the Pola + BR arm achieved some response, compared with 32.5% in the BR arm.

Figure 2: Progression free survival in pivotal trial (Study GO2965)



Pola + BR was associated with a reduced risk of a disease progression event, with a hazard ratio (HR) of 0.38 (95% CI: 0.22 to 0.66). Median PFS was 9.5 months in the Pola + BR group.

The clinical evaluator has concluded that there is sufficient evidence of the efficacy of Polivy given the rarity of refractory DLBCL, which would make a Phase III trial difficult.

Safety

Safety data is limited to that in the clinical studies, none of which assessed safety as a primary outcome.

Table 4: Exposure to polatuzumab and comparators in clinical studies

Study ID	Polatuzumab + BR	BR	Other polatuzumab	Total polatuzumab
GO29365	89	80	52	141
GO29365 (Arm G)	25	-	-	25
DCS4968g	-	-	95	95
GO27834			167	167
GO29044	-	-	82	82

Study ID	Polatuzumab + BR	BR	Other polatuzumab	Total polatuzumab
Total	114	80	396	510

In the three ongoing studies, a further 108 subjects were treated with polatuzumab. None of these received the proposed polatuzumab + BR regimen.

The adverse events which occurred more commonly in patients receiving Pola + BR than BR in the pivotal efficacy study included:

- cytopaenias; neutropaenia; and anaemia;
- gastrointestinal (GIT) events; diarrhoea, decreased appetite, vomiting, upper abdominal pain, dysgeusia, dehydration, oropharyngeal pain;
- neuropathy-type events; peripheral neuropathy, peripheral sensory neuropathy, muscular weakness, paraesthesiae;
- central nervous system (CNS) events; headache, insomnia;
- hypokalaemia and hypophosphataemia;
- fatigue;
- pyrexia;
- pneumonia; and
- elevations of aspartate aminotransferase (AST).

Grade 3 or 4 adverse events (AE) were reported in 84.4% of patients treated with Pola + BR in the pivotal efficacy study compared to 71.8% treated with BR alone. Those which occurred more frequently in the Pola + BR arm were:

- cytopaenias; neutropaenia; and anaemia;
- infections; pneumonia and sepsis;
- hypokalaemia;
- fatigue; and
- hypertension.

Discontinuation due to any AE was reported in 31.1% of Pola + BR patients compared to 15.4% of BR patients.

The incidence of fatal AEs was 20.0% in Pola + BR treated patients compared with 28.2% in BR treated patients. Treatment related deaths were due to infections and pulmonary oedema, myelodysplastic syndrome, progressive multi-focal leukoencephalopathy. The latter (PML) occurred in 1 patient treated with Pola + bendamustine + obinutuzumab in a non-pivotal trial.

The clinical evaluator has noted that Polivy is associated with increased toxicity compared with BR alone. However, in the context of the poor prognosis for relapsed/refractory DLBCL this is an acceptable safety profile if there is an increased degree of efficacy.

Risk management plan

The sponsor submitted EU-RMP version 1.0 (17 December 2018; data lock point 7 September 2018) and ASA version 1.0 (February 2019) in support of this application. In

response to rolling questions sent 8 July 2019, the sponsor updated the ASA to version 1.1 (June 2019).

The risk management plan (RMP) evaluator has recommended conditions of registration consistent with ongoing pharmacovigilance.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies which have been agreed to during evaluation are summarised below in Table 5.[1]

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Myelosuppression (Neutropaenia, Thrombocytopaenia, Anaemia)	ü	–	ü	–
	Peripheral neuropathy	ü	–	ü	–
	Infections	ü	–	ü	–
Important potential risks	Progressive Multifocal Leukoencephalopathy	ü	–	ü	–
	Tumour Lysis Syndrome	ü	–	ü	–
	Embryo-fetal toxicity	ü	–	ü	–
	Hepatic toxicity	ü	–	ü	–
	Carcinogenicity	ü	–	ü	–
Missing information	Use in patients with hepatic impairment	ü	–	ü	–
	Use in patients with renal impairment	ü	–	ü	–
	Use in elderly patients	ü	–	ü	–

[1] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
  Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
	Use in paediatric patients	ü	–	ü	–
	Use in pregnancy	ü*	–	ü	–

* Non-product specific adverse drug reaction follow-up forms

Risk-benefit analysis

Delegate's considerations

The data on Polivy indicates that it offers a clinically significant response in refractory patients, based on the CR outcomes of the pivotal Study G029365. While this is a small trial, the refractory patient population who are unsuitable for ASCT currently has a poor prognosis. Polivy offers a potentially beneficial addition to therapy in this group.

The FDA indication has specified patients who have not responded to two previous therapies. The inclusion criteria for Study G029365 required patients to have received at least one prior therapy, but the median number of previous therapies in the pivotal study was 2 (29% having received 1 prior, 25% having received 2 prior and 46% having received 3 or more prior therapies. The clinical evaluator has noted, however, that overall numbers in this study were small and recommends that the indication remain 'agnostic' to the number of previously failed therapies. The Delegate agrees with this approach.

The Delegate considers the most relevant issue for registration to be the immaturity of the data supporting efficacy for this product. While there is adequate demonstration of a clinically beneficial effect from Pola + BR, there is significant uncertainty as to the scale of that effect. The 95% confidence interval for the difference in CR response rate between Pola + BR and BR alone is from 2.6% to 40.2%.

The Delegate considers the uncertainly in the scale of additional effectiveness offered by Pola + BR compared to BR alone to be significant because the Pola + BR combination imposes an additional burden of toxicity on patients compared to BR alone. If the true additional efficacy benefit were to be at the 'low' end this may alter than risk-benefit assessment of therapy with Pola + BR. Toxicity also has the potential to influence compliance with therapy and overall survival results in the long term.

The FDA approval is based on a rapid assessment and two larger efficacy trials are expected, Studies GO39942 and MO40598, which will clarify overall survival and have larger numbers of patients. The sponsor has indicated that Study GO39942 completed enrolment in June 2019 and a study report is expected in 2021, while Study MO40598 commences enrolment in late 2019.

The Delegate notes that the sponsor has not requested 'provisional' registration of Polivy in Australia, but has concluded that a) the provisional nature of the data supporting the efficacy of Polivy should be effectively communicated in the PI and that b) it is essential that confirmatory trials are made available for evaluation at the earliest opportunity.

The US product information has the advantage of making this plain in the indication with the statement:

Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The Delegate feels that this would make the Australian indication overly complex and, in fact, the Therapeutic Goods Act (1989) does not require further data to support registration per se. However, the Delegate proposes to amend the *Clinical Trials* section of the PI in accordance with the US prescribing information to read in total, with allowance for renumbering for formatting:

'14 CLINICAL STUDIES

14.1 Relapsed or Refractory Diffuse Large B-cell Lymphoma

The efficacy of POLIVY was evaluated in Study GO29365 (NCT02257567), an open-label, multicenter clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL after least one prior regimen. Patients were randomized 1:1 to receive either POLIVY in combination with bendamustine and a rituximab product (BR) or BR alone for six 21-day cycles. Randomization was stratified by duration of response (DOR) to last therapy. Eligible patients were not candidates for autologous HSCT at study entry. The study excluded patients with Grade 2 or higher peripheral neuropathy, prior allogeneic HSCT, active central nervous system lymphoma, or transformed lymphoma.

Following premedication with an antihistamine and antipyretic, POLIVY was given by intravenous infusion at 1.8 mg/kg on Day 2 of Cycle 1 and on Day 1 of Cycles 2–6. Bendamustine was administered at 90 mg/m^2 intravenously daily on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2–6. A rituximab product was administered at a dose of 375 mg/m^2 intravenously on Day 1 of Cycles 1–6. The cycle length was 21 days.

Of the 80 patients randomized to receive POLIVY plus BR (n = 40) or BR alone (n = 40), the median age was 69 years (range: 30–86 years), 66% were male, and 71% were white. Most patients (98%) had DLBCL not otherwise specified. The primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%), and prior transplant failure (20%). The median number of prior therapies was 2 (range: 1–7), with 29% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Eighty percent of patients had refractory disease to last therapy.

In the POLIVY plus BR arm, patients received a median of 5 cycles, with 49% receiving 6 cycles. In the BR arm, patients received a median of 3 cycles, with 23% receiving 6 cycles.

Efficacy was based on complete response (CR) rate at the end of treatment and DOR, as determined by an independent review committee (IRC). Other efficacy measures included IRC-assessed best overall response.

Response rates are summarised in Table 6.

Table 6: Response rates in patients with relapsed or refractory DLBCL

Response per IRC, n (%)a	Polivy + BR n = 40	BR n = 40
Objective Response at End of Treatmentb (95% CI)	18 (45) (29, 62)	7 (18) (7, 33)
CR (95% CI)	16 (40) (25, 57)	7 (18) (7, 33)

Response per IRC, n (%)a	Polivy + BR n = 40	BR n = 40
Difference in CR rates, % (95% CI)c	**22 (3, 41)**	
Best Overall Response of CR or PRd (95% CI)	25 (63) (46, 77)	10 (25) (13, 41)
Best Response of CR (95% CI)	20 (50) (34, 66)	9 (23) (11, 38)

PR = partial remission. a PET-CT based response per modified Lugano 2014 criteria. Bone marrow confirmation of PET-CT CR was required. PET-CT PR required meeting both PET criteria and CT criteria for PR. b End of treatment was defined as 6–8 weeks after Day 1 of Cycle 6 or last study treatment. cMiettinen-Nurminen method d PET-CT results were prioritised over CT results.

In the Polivy plus BR arm, of the 25 patients who achieved a partial or complete response, 16 (64%) had a DOR of at least 6 months, and 12 (48%) had a DOR of at least 12 months. In the BR arm, of the 10 patients who achieved a partial or complete response, 3 (30%) had a DOR lasting at least 6 months, and 2 (20%) had a DOR lasting at least 12 months.'

The Delegate is of the view that the inclusion of non-significant comparator data in the draft Australian product information has a significant potential to mislead clinicians as to the basis for regulatory approval, and of the scope of the data which supports the efficacy of Polivy in a statistically verifiable manner.

Conclusion

The Delegate proposes to include polatuzumab vedotin in the Australian Register of Therapeutic Goods (ARTG) with the indication:

> *Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.*

Following PI amendments, the Delegate proposes to include the following as conditions of the registration:

- The sponsor will provide a study report of trial GO39942 to the TGA for evaluation no later than this trial is first submitted to either the US FDA, European Medicines Agency (EMA) or Health Canada.
- The Register entry will include as a condition of registration a shelf-life of 12 months at 2 to 8 degrees centigrade as specified in the biological evaluation.

Request for ACM advice

The Delegate did not refer this application to the Advisory Committee on Prescription Medicines (ACM) for advice.

Advisory Committee Considerations[2]

The Delegate did not refer this application to the Advisory Committee on Prescription Medicines (ACM) for advice.

[2] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Polivy (polatuzumab vedotin) 140 mg powder for injection vial for, indicated for:

> *Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.*

Specific conditions of registration applying to these goods

1. Polivy (polatuzumab vedotin) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Polivy must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
2. The Polivy European Union-Risk Management Plan (EU-RMP) (version 1.0, dated 17 December 2018, data lock point 7 September 2018), with Australian Specific Annex (version 1.1, dated June 2019), included with submission PM-2019-00471-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two periodic safety update reports (PSURs) each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

   The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
3. Batch release testing and compliance with Certified Product Details (CPD)
   - It is a condition of registration that all batches of Polivy imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
   - It is a condition of registration that up to 5 initial batches of Polivy imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
   - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

4. Certified Product Details

   The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

   The CPD should be emailed to Biochemistry.Testing@health.gov.au as a single PDF document.

5. The sponsor will provide a study report of trial GO39942 to Therapeutic Goods Administration for evaluation no later than this trial is first submitted to either the United States (US) Food and Drug Administration (FDA), European Medicines Agency (EMA) or Health Canada.

6. The register entry will include as a condition of registration a shelf life of 12 months at 2 to 8 degrees centigrade as specified in the Biological evaluation.

7. For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Polivy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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