

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at <https://www.tga.gov.au/reporting-problems>.

AUSTRALIAN PRODUCT INFORMATION – POLIVY (polatuzumab vedotin)

1 NAME OF THE MEDICINE

Polatuzumab vedotin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial is designed to deliver a total of 140 mg of polatuzumab vedotin.

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

POLIVY is a preservative-free white to grayish-white lyophilized powder supplied in single-dose 20 mL vials that deliver 140 mg of polatuzumab vedotin. Upon reconstitution POLIVY concentrate contains 20 mg/mL of polatuzumab vedotin for intravenous infusion (refer to section 4.2 *Dose and method of administration, Method of administration*).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is POLIVY.

POLIVY therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.

POLIVY must be reconstituted and diluted using aseptic techniques under the supervision of a healthcare professional. POLIVY should be administered as an intravenous infusion through a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 µm pore size) and catheter (see 4.2 *Dose and method of administration, Method of administration*). Do not administer as an IV push or bolus.

For information on rituximab or bendamustine, refer to their respective full prescribing information. Refer to Table 1 for dose modification recommendations for neutropenia and thrombocytopenia.

Dose

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. POLIVY, bendamustine, and rituximab can be administered in any order on Day 1 of each cycle. The recommended dose of bendamustine is 90 mg/m²/day on Day 1 and 2 when administered with POLIVY and rituximab.

If not already premedicated, administer premedication with an antihistamine and anti-pyretic to patients prior to administration of POLIVY. The initial dose of POLIVY should be administered as a 90-minute intravenous infusion. Patients should be monitored for infusion-related reactions during the infusion and for at least 90 minutes following completion of the initial dose. If the prior infusion was well tolerated, the subsequent dose of POLIVY may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion.

Duration of Treatment

The recommended duration of treatment is for 6 cycles.

Delayed or Missed Doses

If a planned dose of POLIVY is missed, it should be administered as soon as possible and the schedule of administration should be adjusted to maintain a 21-day interval between doses.

Dose Modifications

The infusion rate of POLIVY should be slowed or interrupted if the patient develops an infusion-related reaction. Discontinue POLIVY immediately and permanently if the patient experiences a life-threatening reaction.

For dose modifications for peripheral neuropathy see Table 1.

Table 1 POLIVY dose modifications for Peripheral Neuropathy, Infusion-related reactions and Myelosuppression.

Severity on Day 1 of any cycle	Dose modification
--------------------------------	-------------------

Attachment 1: Product AusPAR for Polivy (polatuzumab vedotin) Roche Products Pty Limited PM-2019-00471-1-6 Final 3 December 2019. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

Grade 2-3 Hold POLIVY
Peripheral
Neuropathy

Grade 3-4 Thrombocytopenia	<p>Hold all treatment until platelets recover to $>75,000 \text{ mL}$.</p> <p>If platelets recover to $>75,000 \text{ mL}$ on or before Day 7, resume all treatment without any additional dose reductions.</p> <p>If platelets recover to $>75,000 \text{ mL}$ after Day 7:</p> <ul style="list-style-type: none"> restart all treatment, with a dose reduction of bendamustine from 90 mg/m^2 to 70 mg/m^2 or 70 mg/m^2 to 50 mg/m^2 if a bendamustine dose reduction to 50 mg/m^2 has already occurred, discontinue all treatment
-------------------------------	---

^aIf primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.

Special populations

Paediatric populations

The safety and efficacy of POLIVY in children and adolescents (<18 years) has not been established (see section 5.2 *Pharmacokinetics in special populations*).

Elderly

No dose adjustment of POLIVY 65 years of age (see section 5.2 *Pharmacokinetics in special populations*).

Renal Impairment

No dose adjustment of POLIVY is required in patients with creatinine clearance (CrCL) (see section 5.2 *Pharmacokinetics in special populations*).

Hepatic Impairment

No dose adjustment of POLIVY is required for patients with AST or ALT up to $2.5 \times \text{ULN}$ or total bilirubin up to $1.5 \times \text{ULN}$. A recommended dose has not been determined for patients with AST $>2.5 \times \text{ULN}$ or ALT $>2.5 \times \text{ULN}$, total bilirubin $>1.5 \times \text{ULN}$, or patients with a liver transplant (see section 5.2 *Pharmacokinetics in special populations*).

Method of Administration

POLIVY must be reconstituted using sterile water for injection and diluted into an IV infusion bag containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose by a healthcare professional prior to administration.

Use aseptic technique for reconstitution and dilution of POLIVY. Appropriate procedures for the preparation of antineoplastic products should be used.

The reconstituted product contains no preservative and is intended for single-dose usage only. Discard any unused portion.

A dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 µm pore size) and catheter must be used to administer diluted POLIVY.

Reconstitution

1. Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection into the 140 mg POLIVY vial to yield a single-dose solution containing 20 mg/mL polatuzumab vedotin. Direct the stream toward the wall of the vial and not directly on the lyophilized cake.
2. Swirl the vial gently until completely dissolved. *Do not shake*
3. Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, cloudy, or contains visible particulates.

To reduce microbiological hazard, the reconstituted solution should be used as soon as practicable after preparation. If storage is necessary, the reconstituted solution is stable for up to 72 hours at 2°C to 8°C and up to 20 hours at room temperature (9°C to 25°C).

Dilution

1. Polatuzumab vedotin must be diluted to a final concentration of 0.72 – 2.7 mg/mL in an IV infusion bag with a minimum volume of 50mL containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose.
2. Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose:

$$\text{Volume} = \frac{\text{POLIVY dose (1.8 or 1.4 mg/kg)} \times \text{patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/mL)}}$$

3. Withdraw the required volume of reconstituted solution from the POLIVY vial using a sterile syringe and dilute into the IV infusion bag. Discard any unused portion left in the vial.
4. Gently mix the IV bag by slowly inverting the bag. *Do not shake*.
5. Inspect the IV bag for particulates and discard if present.

To reduce microbiological hazard, the prepared solution for infusion should be used as soon as practicable after preparation. If storage is necessary, the solution for infusion may be held for the storage times provided in Table 2. . Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight*.

Table 2 Maximum Allowable Storage Times of the Solution for Infusion Prior to Administration

Diluent used to prepare solution for infusion	Solution for infusion storage conditions ¹
0.9% Sodium Chloride	Up to 24 hours at 2°C to 8°C or up to 4 hours at room temperature (9°C to 25°C)
0.45% Sodium Chloride	Up to 36 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)
5% Dextrose	Up to 72 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)

¹To ensure product stability, do not exceed specified storage durations.

Avoid transportation of the prepared solution for infusion as agitation stress can result in aggregation. If the prepared solution for infusion will be transported, remove air from the infusion bag and limit transportation to 30 minutes at 9°C to 25°C or 12 hours at 2°C to 8°C. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion. The total storage plus transportation times of the diluted product should not exceed the storage duration specified in Table 3.

The product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

POLIVY is contraindicated in patients with a known hypersensitivity to polatuzumab vedotin or any of the excipients

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Myelosuppression

Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with POLIVY as early as the first cycle of treatment (see section 4.8 *Adverse Effects (Undesirable effects)*). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with POLIVY (see section 4.8 *Adverse Effects (Undesirable effects)*). Complete blood counts should be monitored prior to each dose of POLIVY. More frequent lab monitoring and/or POLIVY delays or discontinuation should be considered in patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see section 4.2 *Dose and method of administration*).

Peripheral Neuropathy

Peripheral neuropathy has been reported in patients treated with POLIVY as early as the first cycle of treatment, and the risk increases with sequential doses (see section 4.8 *Adverse Effects (Undesirable effects)*). Patients with pre-existing peripheral neuropathy may experience worsening of this condition. Peripheral neuropathy reported with POLIVY treatment is predominantly sensory peripheral neuropathy; however, motor and sensorimotor peripheral neuropathy have also been reported. Patients should be monitored for symptoms of peripheral neuropathy such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain,

burning sensation, weakness, or gait disturbance. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of POLIVY (see section 4.2 *Dose and method of administration*).

Infections

Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including *pneumocystis jirovecii* and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with POLIVY (see section 4.8 *Adverse Effects (Undesirable effects)*). Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections. Anti-infective prophylaxis should be considered. POLIVY and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported with POLIVY treatment (see section 4.8 *Adverse Effects (Undesirable effects)*). Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. POLIVY and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumor Lysis Syndrome

Patients with high tumor burden and rapidly proliferative tumor may be at increased risk of tumor lysis syndrome. Appropriate measures in accordance with local guidelines should be taken prior to treatment with POLIVY. Patients should be monitored closely for tumor lysis syndrome during treatment with POLIVY.

Embryofetal toxicity

Based on the mechanism of action and nonclinical studies, POLIVY can be harmful to the fetus when administered to a pregnant woman. (see section 4.6 *Fertility, Pregnancy and Lactation*). Advise a pregnant woman of the risk to the fetus.

Females of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 9 months after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 6 months after the last dose (see section 4.6 *Fertility, Pregnancy and Lactation*).

Hepatic Toxicity

Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with POLIVY. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Liver enzymes and bilirubin level should be monitored.

Use in hepatic impairment

The safety and efficacy of POLIVY in patients with AST $>2.5 \times \text{ULN}$, ALT $>2.5 \times \text{ULN}$ or total bilirubin $>1.5 \times \text{ULN}$ has not been formally studied. Monitor these patients for adverse events after treatment (see sections 4.2 *Special populations* and 5.2 *Pharmacokinetics in special populations*).

Use in renal impairment

The safety and efficacy of POLIVY in patients with CrCL <30 mL/min has not been formally studied (see sections 4.2 *Special populations* and 5.2 *Pharmacokinetics in special populations*).

Use in the elderly

No overall differences in safety or efficacy w 65 years of age and younger patients (see sections 4.2 *Special populations* and 5.2 *Pharmacokinetics in special populations*).

Paediatric use

The safety and efficacy of POLIVY in children and adolescents below 18 years of age has not been established (see sections 4.2 *Special populations* and 5.2 *Pharmacokinetics in special populations*).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No dedicated clinical drug-drug interaction studies with POLIVY in humans have been conducted.

Drug interactions with co-medications that are CYP3A inhibitors, inducers or substrates

Based on physiologically-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Monitor patients receiving concomitant strong CYP3A inhibitors more closely for signs of toxicities. Strong CYP3A inducers (e.g., rifampicin) may decrease the AUC of unconjugated MMAE by 49%.

Unconjugated MMAE is not predicted to alter the AUC of concomitant drugs that are CYP3A substrates (e.g., midazolam).

Co-administration with other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of MMAE-mediated inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. MMAE does not induce CYP1A2, CYP2B6 or CYP3A4/5 *in vitro*.

Co-administration with Drugs that are Substrates of Transporters

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations. MMAE was not an *in vitro* substrate or inhibitor for the BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3 or OCT2 transporters. MMAE was also not an *in vitro* inhibitor of BSEP or OAT1.

Drug interactions of rituximab and bendamustine in combination with polatuzumab vedotin

The pharmacokinetics (PK) of rituximab and bendamustine are not affected by co-administration with POLIVY. Concomitant rituximab is associated with increased antibody conjugated MMAE (acMMAE) plasma AUC by 24% and decreased unconjugated MMAE plasma AUC by 37%, based on population PK analysis. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of POLIVY on human male and female fertility have not been studied. However, results from a repeat-dose toxicity study in rats indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. In the 4-week repeat-dose toxicity study in rats with weekly IV dosing of 2, 6, and 10 mg/kg, dose-dependent testicular seminiferous tubule degeneration with abnormal lumen contents in the epididymis was observed. Findings in the testes and epididymis did not reverse following a 6-week treatment-free period and correlated with decreased testes weight and gross findings of small and/or soft testes at recovery necropsy in males given doses \geq 2 mg/kg. A no effect level was not established. Although there were no histological abnormalities in female reproductive organs from animal studies, dedicated fertility studies in female animals were not conducted. MMAE, the main active catabolite of polatuzumab vedotin, has been shown to have aneugenic properties in an *in vivo* rat bone marrow micronucleus study. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

Therefore, men being treated with POLIVY are advised to have sperm samples frozen and stored before treatment. Men being treated with POLIVY are advised to use effective contraception during treatment with POLIVY and not to father a child during treatment and for up to 6 months following the last dose. Effects on spermatogenesis cannot be excluded after a 6 month treatment-free period.

Use in pregnancy - Category D

There are no adequate or well-controlled studies with POLIVY in pregnant women. However, based on its mechanism of action and findings in animals, POLIVY can cause fetal harm when administered to a pregnant woman.

Embryofetal lethality and toxicity were seen in a rat embryofetal development study in which pregnant rats received two IV doses of 0.2 mg/kg MMAE, the main active metabolite of polatuzumab vedotin, during the period of organogenesis, and included an increased incidence of post-implantation loss, and an increase in the incidence of fetal malformations including protruding tongue, malrotated hindlimbs, gastroschisis and agnathia. These adverse embryofetal development effects occurred at exposures less than that expected in patients receiving polatuzumab vedotin.

POLIVY should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the fetus.

Females of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 9 months after the last dose.

See the 'Effects on fertility' section above pertaining to advice for women whose male partners are being treated with POLIVY.

Use in lactation

It is not known whether polatuzumab vedotin or its metabolites are excreted in human breast milk. No studies have been conducted to assess the impact of POLIVY on milk production or its presence in breast milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants due to POLIVY, women should discontinue breastfeeding during POLIVY treatment.

Contraception

Females of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 9 months after the last dose.

Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 6 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

POLIVY may have a minor influence on the ability to drive and use machines. Infusion related reactions, peripheral neuropathy, fatigue, and dizziness may occur during treatment with POLIVY (see section 4.4 *Special warnings and precautions for use* and 4.8 *Adverse effects (Undesirable effects)*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

For the clinical development program of POLIVY as a whole, an estimated total of 588 patients have received POLIVY. The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up of previously treated diffuse large B-cell lymphoma (DLBCL) patients from the pivotal clinical trial GO29365. This includes run-in phase patients (n=6) and randomized patients (n=39) who received POLIVY in combination with bendamustine and rituximab (BR) compared to randomized patients (n=39) who received BR alone. Randomized patients in the POLIVY treatment arm received a median of 5 cycles of treatment while randomized patients in the comparator arm received a median of 3 cycles of treatment.

The most frequently- POLIVY in combination with BR were anemia, thrombocytopenia, neutropenia, fatigue, diarrhea, nausea, and pyrexia. Serious adverse events were reported in 64.4% of POLIVY plus BR treated patients which

included febrile neutropenia (11.1%), pyrexia (8.9%), pneumonia (8.9%), anemia (4.4%), duodenal ulcer hemorrhage (4.4%), sepsis (4.4%), and thrombocytopenia (4.4%) [36].

ADRs leading to treatment regimen discontinuation in >5% of patients were thrombocytopenia (8.9%) and neutropenia (6.7%).

The following categories of frequency have been used:

Table 3 Summary of adverse drug reactions occurring in previously treated DLBCL patients treated with POLIVY in combination with BR

System Order Class/ ADR (MedDRA Preferred Term)	POLIVY + bendamustine + rituximab N = 45		Frequency (all grades)	Bendamustine + rituximab N=39		Frequency (all grades)
	All grades (%)	Grades 3-4 (%)		All grades (%)	Grades 3-4 (%)	
Infections and Infestations						
Pneumonia ^a	15.6	6.7	Very common	10.3	0	Very common
Blood and Lymphatic System Disorders						
Anaemia	46.7	24.4	Very common	25.6	17.9	Very common
Neutropenia	46.7	40.0	Very common	38.5	33.3	Very common
Thrombocytopenia	46.7	37.8	Very common	28.2	23.1	Very common
Febrile Neutropenia	11.1	11.1	Very common	12.8	12.8	Very common
Leukopenia	11.1	6.7	Very common	12.8	7.7	Very common
Lymphopenia	11.1	11.1	Very common	0	0	Rare
Metabolism and Nutrition Disorders						
Decreased appetite	26.7	2.2	Very common	20.5	0	Very common
Hypokalemia	15.6	6.7	Very common	7.7	2.6	Common
Hypoalbuminemia	13.3	2.2	Very common	5.1	0	Common
Hypocalcemia	11.1	2.2	Very common	2.6	0	Common
Nervous System Disorders						
Neuropathy Peripheral	20.0	0	Very common	2.6	0	Common
Dizziness	13.3	0	Very common	7.7	0	Common
Peripheral Sensory neuropathy	13.3	0	Very common	0	0	Rare

System Order Class/ ADR (MedDRA Preferred Term)	POLIVY + bendamustine + rituximab N = 45		Frequency (all grades)	Bendamustine + rituximab N=39		Frequency (all grades)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	15.6	0	Very common	20.5	0	Very common
Gastrointestinal Disorders						
Diarrhea	37.8	4.4	Very common	28.2	5.1	Very common
Nausea	33.3	0	Very common	41.0	0	Very common
Constipation	17.8	0	Very common	20.5	2.6	Very common
Vomiting	17.8	2.2	Very common	12.8	0	Very common
Abdominal Pain	11.1	4.4	Very common	10.3	2.6	Very common
Abdominal Pain Upper	11.1	2.2	Very common	5.1	0	Common
Skin and Subcutaneous Tissue Disorders						
Pruritis	13.3	0	Very common	10.3	2.6	Very common
General Disorders and Administration Site Conditions						
Fatigue	40.0	4.4	Very common	35.9	2.6	Very common
Pyrexia	33.3	2.2	Very common	23.1	0	Very common
Asthenia	11.1	0	Very common	15.4	0	Very common
Chills	11.1	0	Very common	7.7	0	Common
Investigations						
Weight decreased	15.6	2.2	Very common	7.7	2.6	Common
Injury, Poisoning, and Procedural						
Infusion-related reaction ^b	33.3	6.7	Very common	23.1	10.3	Very common

^aADR associated with fatal outcome

^bDefined as all adverse events reported as related to study treatment within 24 hours after treatment infusion

8.9% of patients in the POLIVY plus BR arm discontinued POLIVY due to neutropenia compared to 2.6% of patients in the BR arm who discontinued treatment due to neutropenia. Thrombocytopenia events led to discontinuation of treatment in 11.1% of patients in the POLIVY plus BR arm and 5.1% of patients in the BR arm. No patients discontinued treatment due to anemia in either the POLIVY plus BR arm or BR arm.

In the POLIVY plus BR arm, Grade 1 and 2 peripheral neuropathy events were reported in 26.7% and 13.3% of patients, respectively. In the BR arm, Grade 1 and 2 peripheral neuropathy events were reported in 2.6% and 5.1% of patients, respectively. No Grade 3-5 peripheral neuropathy events were reported in either the POLIVY plus BR arm or BR arm. 2.2% of patients discontinued POLIVY treatment due to peripheral neuropathy and 4.4% of patients had POLIVY dose reduction due to peripheral neuropathy. No patients in the BR arm discontinued treatment or had dose reductions due to peripheral neuropathy. In the POLIVY plus BR arm, the median onset to first event of peripheral neuropathy was 1.8 months, and 61.1% of patients with peripheral neuropathy events reported event resolution (see 4.4 *Special warnings and precautions for use*).

Infections, including pneumonia and other types of infections, were reported in 53.3% of patients in the POLIVY plus BR arm and 51.3% of patients in the BR arm. In the POLIVY plus BR arm, serious infections were reported in 28.9% of patients and fatal infections were reported in 8.9% of patients. In the BR arm, serious infections were reported in 30.8% of patients and fatal infections were reported in 10.3% of patients. One patient (2.2%) discontinued treatment in the POLIVY plus BR arm due to infection compared to 5.1% of patients in the BR arm (see 4.4 *Special warnings and precautions for use*).

One case of PML, which was fatal, occurred in a patient treated with POLIVY plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies (see 4.4 *Special warnings and precautions for use*).

In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible (see 4.4 *Special warnings and precautions for use*).

Gastrointestinal toxicity events were reported in 80.0% of patients in the POLIVY plus BR arm compared to 64.1% of patients in the BR arm [41]. Most events were Grade 1-2, and Grade 3-4 events were reported in 22.2% of patients in the POLIVY plus BR arm compared to 12.8% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhea and nausea [42].

Laboratory abnormalities

All identified laboratory abnormalities were reported as ADRs, refer to Table 4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose in human clinical trials. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers an anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 (IgG1) monoclonal antibody via a cleavable linker. The monoclonal antibody binds with nanomolar affinity and selectivity to CD79b, a cell surface component of the B-cell receptor. CD79b expression is restricted to normal cells within the B-cell lineage (with the exception of plasma cells) and malignant B-cells; it is expressed in > 95% of DLBCL. Upon binding CD79b, polatuzumab vedotin is internalized and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Clinical trials

The efficacy of POLIVY was evaluated in Study GO29365, an open-label, multicenter clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL after at 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/m² 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/m² 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 summarized in Table 4

Table 4 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 Treatment^b (95% CI)	18 (45) (29, 62)	7 (18) (7, 33)
CR (95% CI)	16 (40) (25, 57)	7 (18) (7, 33)
Difference in CR rates, % (95% CI) ^c	22 (3, 41)	
Best Overall Response of CR or PR^d (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.

^c Miettinen-Nurminen method.

^d PET-CT results were prioritized 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.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. Across all arms of study GO29365, 8 out of 134 (6.0%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Across all seven clinical studies, 14 out of 536 (2.6%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Due to the limited number of anti-polatuzumab vedotin antibody positive patients, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to polatuzumab vedotin with the incidence of antibodies to other products may be misleading.

5.2 PHARMACOKINETIC PROPERTIES

Antibody-conjugated MMAE (acMMAE) plasma exposure increased dose-proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. After the first 1.8 mg/kg polatuzumab vedotin dose, the acMMAE mean maximum concentration (C_{\max}) was 803 (\pm 233) ng/mL and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 1860 (\pm 966) day*ng/mL. Based on the population PK analysis, Cycle 3 acMMAE AUC increased by approximately 30% over cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. The terminal half-life at cycle 6 was approximately 12 days (95% CI of 8.1-19.5 days) for acMMAE.

Exposures of unconjugated MMAE, the cytotoxic component of polatuzumab vedotin, increased dose proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. MMAE plasma concentrations followed formation rate limited kinetics. After the first 1.8 mg/kg polatuzumab vedotin dose, the C_{\max} was 6.82 (\pm 4.73) ng/mL, the time to maximum plasma concentration is approximately 2.5 days, and the terminal half-life is approximately 4 days. Plasma exposures of unconjugated MMAE are <3% of acMMAE exposures [63]. Based on the population PK analysis, there is a decrease of plasma unconjugated MMAE exposure (AUC and C_{\max}) after repeated every-three-week dosing.

Absorption

POLIVY is administered as an IV infusion. There have been no studies performed with other routes of administration.

Distribution

The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume.

In vitro, MMAE is moderately bound (71% - 77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells *in vitro*; the blood to plasma concentration ratio is 0.79 to 0.98.

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations.

Metabolism

Polatuzumab vedotin is expected undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites.

In vitro studies indicate that MMAE is a substrate for CYP 3A4/.

MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Excretion

Based on a population pharmacokinetic analysis, the conjugate (acMMAE) is primarily eliminated by non-specific linear clearance pathway with a value of 0.9 L/day.

In vivo studies in rats dosed with polatuzumab vedotin (radiolabel on MMAE) demonstrate that the majority (95%) of radioactivity is excreted in faeces and the minority (5%) of radioactivity is excreted in urine.

Pharmacokinetics in Special Populations

Elderly

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on a population PK analysis with patients aged 20-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients

Children

No studies have been conducted to investigate the pharmacokinetics of POLIVY in paediatric patients (<18 years old).

Renal Impairment

In patients with mild (CrCL 60-89 mL/min, n=161) or moderate (CrCL 30-59 mL/min, n=109) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with

analysis. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 mL/min, n=3) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis (see section 4.2 *Dose and method of administration*).

Hepatic Impairment

In patients with mild hepatic impairment [AST >1.0 - 2.5×ULN or ALT >1.0 - 2.5×ULN or total bilirubin >1.0 - 1.5×ULN, n=54], acMMAE exposures are similar whereas unconjugated MMAE AUC are 40% higher compared to patients with normal hepatic function (n=399), based on a population pharmacokinetic analysis.

There are insufficient data to assess the impact of moderate hepatic impairment (total bilirubin >1.5 - 3×ULN, n=2) on PK. No data are available in patients with severe hepatic impairment or liver transplantation (see section 4.2 *Dose and method of administration*).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No dedicated mutagenicity studies in animals have been performed with polatuzumab vedotin. MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay

Carcinogenicity

No dedicated carcinogenicity studies in animals have been performed with polatuzumab vedotin and/or MMAE.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Succinic acid, sodium hydroxide, sucrose, polysorbate 20.

6.2 INCOMPATIBILITIES

Do not mix POLIVY with, or administer through the same infusion line, as other medicinal products.

No incompatibilities have been observed between POLIVY and IV infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), or fluorinated ethylene propylene (FEP) or polytetrafluorethylene (PTFE) and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

The reconstituted solution should be used immediately. If the solution is not used immediately, it can be stored no longer than 72 hours at 2°C to 8°C, or 20 hours at ambient temperature.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store unopened vials at 2°C to 8°C.

Keep vial in the outer carton in order to protect from light.

Do not freeze. Do not shake

6.5 NATURE AND CONTENTS OF CONTAINER

POLIVY is available in a single-use glass vial in a pack size of 1 vial.

The POLIVY vial stoppers are not derived from natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container). Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number:

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9 DATE OF FIRST APPROVAL

21 October 2019

10 DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	N/A