# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

Polivy® (polatuzumab vedotin),140 mg, powder for injection via intravenous infusion.

## 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. Polatuzuamab vedotin is produced by recombinant DNA technology in Chinese Hamster Ovary cells).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for injection.

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 must 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 2 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/m$^2$/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**

| Severity on Day 1 of any cycle | Dose modification |
|---|---|
| Grade 2-3 | Hold Polivy dosing until improvement to ≤ Grade 1.<br><br>If recovered to Grade ≤1 on or before Day 14, restart Polivy at a permanently reduced dose of 1.4 mg/kg.<br><br>If a prior dose reduction to 1.4 mg/kg has occurred, discontinue Polivy.<br><br>If not recovered to Grade ≤1 on or before Day 14, discontinue Polivy. |
| Grade 4 | Discontinue Polivy. |

For dose modifications for myelosuppression see Table 2

**Table 2 Polivy, bendamustine, and rituximab dose modifications for myelosuppression**

| Severity on Day 1 of any cycle | Dose modification[a] |
|---|---|
| Grade 3-4 Neutropenia | Hold all treatment until ANC recovers to >1000/μL.<br><br>If ANC recovers to >1000/μL on or before Day 7, resume all treatment without any additional dose reductions.<br><br>If ANC recovers to >1000/μL after Day 7:<br>• 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$^2$<br>• if a bendamustine dose reduction to 50 mg/m$^2$ has already occurred, discontinue all treatment |
| Grade 3-4 Thrombocytopenia | Hold all treatment until platelets recover to >75,000/μL.<br><br>If platelets recover to >75,000/μL on or before Day 7, resume all treatment without any additional dose reductions.<br><br>If platelets recover to >75,000/μL after Day 7:<br>• 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$^2$<br>• if a bendamustine dose reduction to 50 mg/m$^2$ has already occurred, discontinue all treatment |

[a]If 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 is required in patients ≥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) ≥30mL/min. A recommended dose has not been determined for patients with CrCL <30mL/min (see section *5.2 Pharmacokinetics in special populations*).

*Hepatic Impairment*

The administration of Polivy in patients with moderate or severe hepatic impairment (total bilirubin greater than 1.5 × upper limit of normal [ULN]) should be avoided.

No dose adjustment is required for patients with mild hepatic impairment [total bilirubin greater than ULN and less than or equal to 1.5xULN or aspartate transaminase AST greater than ULN] (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.

For instructions on reconstitution and dilution of the product before administration, see section 6.6.

## *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 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 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 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 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 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.

**Embryo-Foetal 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 foetus.

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 (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

**Use in hepatic impairment**

The safety and efficacy of Polivy in patients with AST >2.5×ULN, ALT >2.5×ULN or total bilirubin >1.5×ULN has not been formally studied and these patients are likely to have increased exposure to MMAE. The administration of Polivy in patients with moderate or severe hepatic

impairment (total bilirubin greater than 1.5 × ULN) should be avoided (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 were observed between patients ≥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 Tecentriq 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 physiological-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., rifampin) 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).

*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*

**Fertility**

No dedicated fertility studies in animals have been performed with Polivy. However, results of repeat-dose toxicity 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 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 and correlated with decreased testes weight and gross findings of small and/or soft testes at recovery necropsy in males given doses ≥ 2 mg/kg.

Although there were no histological abnormalities in female reproductive organs from animal studies, dedicated fertility studies in female animals were not conducted.

**Pregnancy**

Polivy is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Polivy can cause fetal harm based on the animal studies and the drug's mechanism of action (see section *5.1 Pharmacodynamic properties*).

**Breast-feeding**

It is not known whether polatuzumab vedotin is 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 and for at least 3 months after the last dose.

**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 Undesirable effects*).

### *4.8 Undesirable Effects*

**Clinical Trials**

For the clinical development program of Polivy as a whole, an estimated total of 1429 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 (n=151) from the pivotal clinical trial GO29365. This includes run-in phase patients (n=6) and randomized patients (n=39) and extension cohort patients (n=106) who received Polivy in combination with bendamustine and rituximab (BR) compared to randomized patients (n=39) who received BR alone. 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-reported (≥30%) ADRs in patients treated with Polivy in combination with BR were anemia, thrombocytopenia, neutropenia, diarrhea, nausea, and peripheral neuropathy. Serious adverse events were reported in 55.6% of Polivy plus BR treated patients which included

the following that occurred in ≥5% of patients: febrile neutropenia (9.3%), pyrexia (7.9%), pneumonia (6.6%), and sepsis (6.6%).

The ADRs leading to treatment regimen discontinuation in >5% of patients was thrombocytopenia (6.0%) and neutropenia (6.7%).

The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

**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 = 151** | | **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] | 14.6 | 9.3 | Very common | 17.9 | 5.1 | Very common |
| Sepsis | 10.6 | 9.9 | Very common | 10.3 | 10.3 | Very common |
| Upper respiratory tract infection | 9.9 | 0.7 | Common | 7.7 | 0 | Common |
| Herpes virus infection | 5.3 | 0.7 | Common | 10.3 | 2.6 | Very common |
| Cytomegalovirus infection | 2.1 | 0.7 | Common | 2.6 | 2.6 | Common |
| **Blood and Lymphatic System Disorders** | | | | | | |
| Anemia | 31.8 | 12.6 | Very common | 28.2 | 17.9 | Very common |
| Neutropenia | 45.7 | 40.4 | Very common | 43.6 | 35.9 | Very common |
| Thrombocytopenia | 32.5 | 25.8 | Very common | 33.3 | 25.6 | Very common |
| Febrile Neutropenia | 11.3 | 10.6 | Very common | 17.9 | 17.9 | Very common |
| Leukopenia | 15.2 | 10.5 | Very common | 23.1 | 18.0 | Very common |
| Lymphopenia | 13.2 | 12.5 | Very common | 7.7 | 7.7 | Common |
| Pancytopenia | 3.3 | 2.0 | Common | 0 | 0 | Very rare |
| **Metabolism and Nutrition Disorders** | | | | | | |
| Decreased appetite | 25.8 | 2.6 | Very common | 20.5 | 0 | Very common |
| Hypokalemia | 16.5 | 6.5 | Very common | 10.3 | 2.6 | Very common |
| Hypoalbuminemia | 6.0 | 1.3 | Common | 7.7 | 0 | Common |
| Hypocalcemia | 5.3 | 0.7 | Common | 5.2 | 0 | Common |
| **Nervous System Disorders** | | | | | | |
| Neuropathy Peripheral | 30.5 | 0.7 | Very common | 7.7 | 0 | Common |

| | | | | | | |
|---|---|---|---|---|---|---|
| Dizziness | 11.3 | 0 | Very common | 7.7 | 0 | Common |
| Peripheral Sensory neuropathy | 7.3 | 0 | Common | 0 | 0 | Very rare |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | |
| Cough | 15.9 | 0 | Very common | 25.6 | 0 | Very common |
| Pneumonitis | 1.3 | 0 | Common | 0 | 0 | Very rare |
| **Gastrointestinal Disorders** | | | | | | |
| Diarrhea | 35.8 | 4.0 | Very common | 28.2 | 5.1 | Very common |
| Nausea | 33.1 | 0.7 | Very common | 41.0 | 0 | Very common |
| Constipation | 18.5 | 0 | Very common | 20.5 | 2.6 | Very common |
| Vomiting | 17.2 | 2.6 | Very common | 12.8 | 0 | Very common |
| Abdominal Pain | 17.9 | 4.6 | Very common | 17.9 | 2.6 | Very common |
| Abdominal Pain Upper | 7.3 | 0.7 | Common | 5.1 | 0 | Common |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | |
| Pruritis | 9.3 | 0 | Common | 10.3 | 2.6 | Very common |
| **Musculoskeletal disorders** | | | | | | |
| Arthralgia | 4.0 | 0 | Common | 0 | 0 | Very rare |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 26.5 | 2.0 | Very common | 35.9 | 2.6 | Very common |
| Pyrexia | 28.5 | 1.3 | Very common | 23.1 | 0 | Very common |
| Asthenia | 11.9 | 2.0 | Very common | 15.4 | 0 | Very common |
| Chills | 4.6 | 0 | Common | 7.7 | 0 | Common |
| **Investigations** | | | | | | |
| Weight decreased | 13.9 | 0.7 | Very common | 7.7 | 2.6 | Common |
| Transaminase elevation | 7.3 | 0.7 | Common | 0 | 0 | Very rare |
| Hypophosphatemia | 4.0 | 1.4 | Common | 2.6 | 2.6 | Common |
| Lipase increased | 4.0 | 1.4 | Common | 0 | 0 | Very rare |
| **Injury, Poisoning, and Procedural** | | | | | | |
| Infusion-related reaction[b] | 11.9 | 2.0 | Very common | 5.1 | 0 | Common |

### *Description of selected adverse drug reactions from clinical trials*

### *Myelosuppression*

4.0% 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 7.9% of patients in the Polivy plus BR arms and 5.1% of patients in the BR arm. No patients discontinued treatment due to anemia in either the Polivy plus BR arms or BR arm.

***Peripheral Neuropathy***

In the Polivy plus BR arm, Grade 1 and 2 peripheral neuropathy events were reported in 15.9% and 12.6% 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. One Grade 3 peripheral neuropathy event was reported in the Polivy plus BR arms and no Grade 3 peripheral neuropathy events were reported in the BR arm. No Grade 4-5 peripheral neuropathy events were reported in either the Polivy plus BR arms or BR arm. 2.6% of patients discontinued Polivy treatment due to peripheral neuropathy and 2.0% 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 arms, the median onset to first event of peripheral neuropathy was 1.6 months, and 39.1% of patients with peripheral neuropathy events reported event resolution (see *4.4 Special warnings and precautions for use*).

***Infections***

Infections, including pneumonia and other types of infections, were reported in 48.3% of patients in the Polivy plus BR arm and 51.3% of patients in the BR arm. In the Polivy plus BR arms, serious infections were reported in 27.2% of patients and fatal infections were reported in 6.6% 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. Four patients (2.6%) discontinued treatment in the Polivy plus BR arms due to infection compared to 2 patients (5.1%) of patients in the BR arm (see *4.4 Special warnings and precautions for use*).

***Progressive Multifocal Leukoencephalopathy (PML)***

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).*

***Hepatic toxicity***

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***

Gastrointestinal toxicity events were reported in 72.2% of patients in the Polivy plus BR arms compared to 66.7% of patients in the BR arm. Most events were Grade 1-2, and Grade 3-4 events were reported in 16.5% of patients in the Polivy plus BR arm compared to `12.9% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhea and nausea.

**Laboratory abnormalities**

All identified laboratory abnormalities were reported as ADRs, refer to Table 3.

**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 in Australia are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and Healthcare professionals in New Zealand are asked to report any suspected adverse events to https://nzphvc.otago.ac.nz/reporting/.

### *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). For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766) (New Zealand).

## 5. PHARMACOLOGICAL PROPERTIES

### *5.1 Pharmacodynamic Properties*

**Mechanism of action**

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent 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 high 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 rapidly 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 plus BR was evaluated in an international, multicenter, open-label study (GO29365) which included a randomized cohort (n=80) and an extension cohort (n=106) of patients with previously treated DLBCL. .

Eligible patients were not candidates for autologous hematopoietic stem cell transplant (HSCT) and had relapsed or refractory disease after receiving at least one prior systemic chemotherapy regimen. The study excluded patients with prior allogeneic HSCT, central nervous system lymphoma, transformed follicular lymphoma (FL), and grade 3b FL.

Polivy was given intravenously at 1.8 mg/kg administered 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. Rituximab was administered at 375 mg/m$^2$ intravenously on Day 1 of Cycles 1-6.

The primary endpoint of the study was complete response (CR) rate at end of treatment (6-8 weeks after day 1 of cycle 6 or last study treatment) as assessed by independent review committee (IRC). Efficacy results are summarized in Table 4-5 and in Figures 1-3.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics . The median age was 69 years (range 30 to 86 years) and 71% of patients were white and 66% were male. The majority of patients (98%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% of patients had germinal center B-cell like (GCB) DLBCL. 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% (n=23) receiving one prior therapy, 25% (n=20) receiving 2 prior therapies, and 46% (n=37) receiving 3 or more prior therapies. 80% of patients had refractory disease.

The primary endpoint of the study was complete response (CR) rate at end of treatment (6-8 weeks after day 1 of cycle 6 or last study treatment) as assessed by independent review committee (IRC). Efficacy results are summarized in Table 4-5 and in Figures 1-3.

**Table 4 Summary of efficacy in patients with previously treated DLBCL from study GO29365**

| | **Polivy + bendamustine + rituximab N= 40** | **Bendamustine + rituximab N= 40** |
|---|---|---|
| | **Median observation time 42 months** | |
| ***Primary Endpoint*** | | |
| Complete Response Rate* (IRC-assessed) at End of treatment** | | |
| Responders (%) | 16 (40.0) | 7 (17.5) |
| Difference in response rate (%) [95% CI] | 22.5 [2.6, 40.2] | |
| p-value (CMH chi-squared test***) | 0.0261 | |
| ***Key Endpoints*** | | |
| Overall Survival | | |
| Number (%) of patients with event | 26 (65.0) | 29 (72.5) |
| Median OS (95% CI), months | 12.4 (9.0, 32) | 4.7 (3.7, 8.3) |
| HR [95% CI] | 0.42 [0.24, 0.75] | |
| p-value (Log-Rank test, stratified***) | 0.0014¶ | |
| Progression Free survival (INV-assessed) | | |
| Number (%) of patients with event | 30 (75.0) | 35 (87.5) |
| Median PFS (95% CI), months | 7.5 (5.0, 17.0) | 2.0 (1.5, 3.7) |
| HR [95% CI] | 0.33 [0.20, 0.56] | |
| p-value (Log-Rank test, stratified***) | <0.0001 | |
| Duration of response (INV-assessed) | | |
| Number of patients included in analysis | 28 | 13 |
| Number (%) of patients with event | 20 (71.4) | 11 (84.6) |
| Median DOR (95% CI), months | 12.7 (5.8, 27.9) | 4.1 (2.6, 12.7) |
| HR [95% CI] | 0.42 [0.19, 0.91] | |
| p-value (Log-Rank test, stratified***) | 0.0245 | |

| | | |
|---|---|---|
| Overall Response Rate* (INV-assessed) at End of Treatment** | | |
| Responders (%) (CR, PR) | 19 (47.5) | 7 (17.5) |
| Difference in response rate (%) [95% CI] | 30.0 [9.5, 47.4] | |
| p-value (CMH chi-squared test***) | 0.0036 | |
| Complete Response (%) (CR) | 17 (42.5) | 6 (15.0) |
| Difference in response rate (%) [95% CI] | 27.5 [7.7, 44.7] | |
| p-value (CMH chi-squared test***) | 0.0061 | |
| Partial Response (%) (PR) | 2 (5.0) | 1 (2.5) |
| 95% CI Clopper-Pearson | [0.6, 16.9] | [0.06, 13.2] |
| Best Overall Response Rate* (INV-assessed) | | |
| Responders (%) [CR, PR] | 28 (70.0) | 13 (32.5) |
| Difference in response rate (%) [95% CI] | 37.5 [15.6, 54.7] | |
| Complete Response (%) [CR] | 23 (57.5) | 8 (20.0) |
| 95% CI Clopper-Pearson | [40.9, 73.0] | [9.1, 35.7] |
| Partial Response (%) [PR] | 5 (12.5) | 5 (12.5%) |
| 95% CI Clopper-Pearson | [4.2, 26.8] | [4.2, 26.8] |

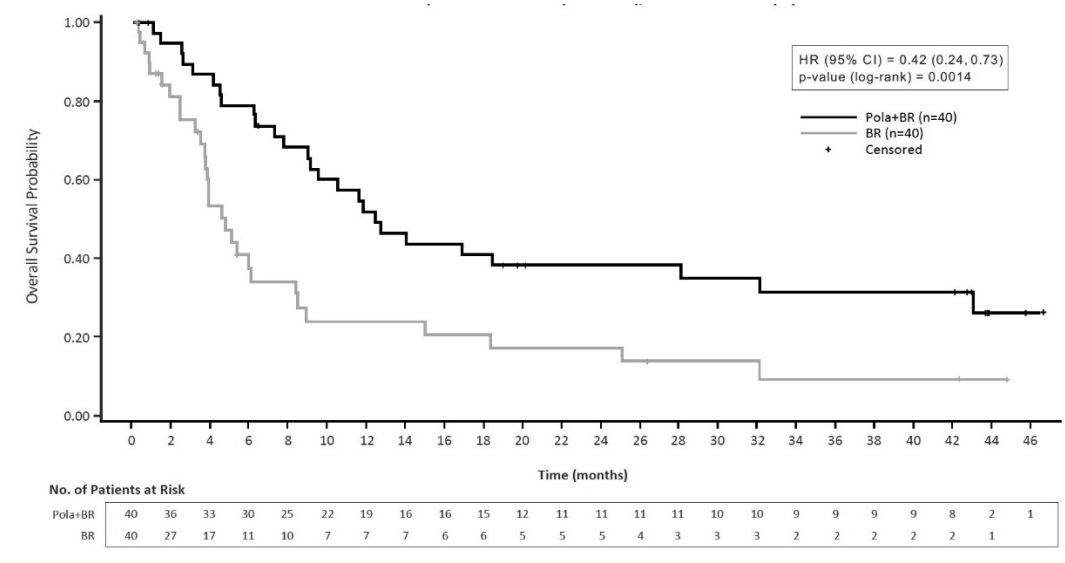
CMH Cochran-Mantel-Haenszel; OS: Overall survival; NE: Not evaluable; PFS: progression free survival; DOR: Duration of response

*Per modified Lugano 2014 criteria: Bone marrow confirmation of PET-CT CR required. PET-CT PR required meeting both PET-CT criteria and CT criteria [56].

**6-8 weeks after day 1 of cycle 6 or last study treatment

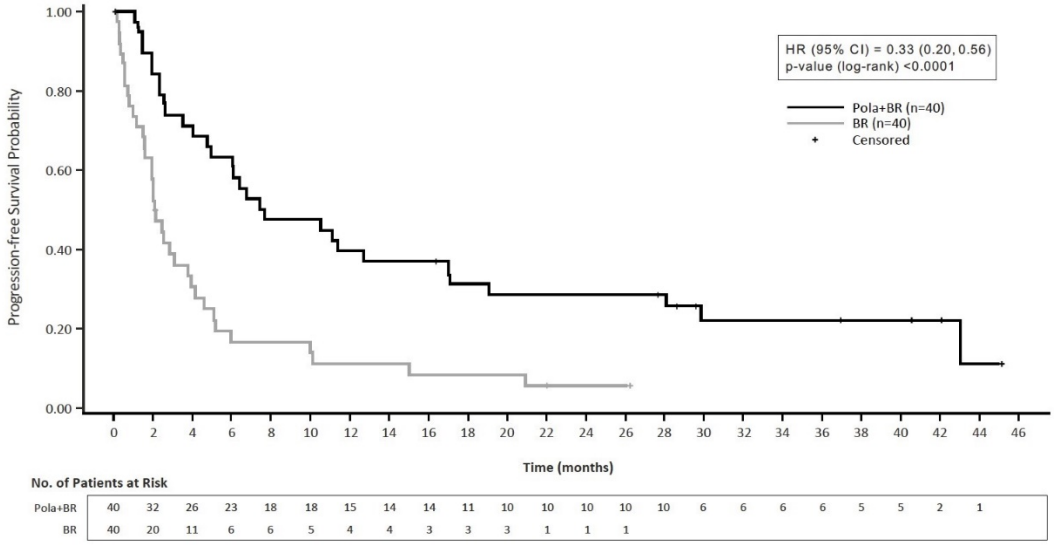
*** Stratification by duration of response to prior therapy (≤12 months vs >12 months)

**Figure 1 Kaplan Meier curve of overall survival**




No.: number; Pola: Polivy; BR: bendamustine and rituximab; HR: hazard ratio. CI: confidence interval

**Figure 2 Kaplan-Meier curve of INV assessed progression-free survival**

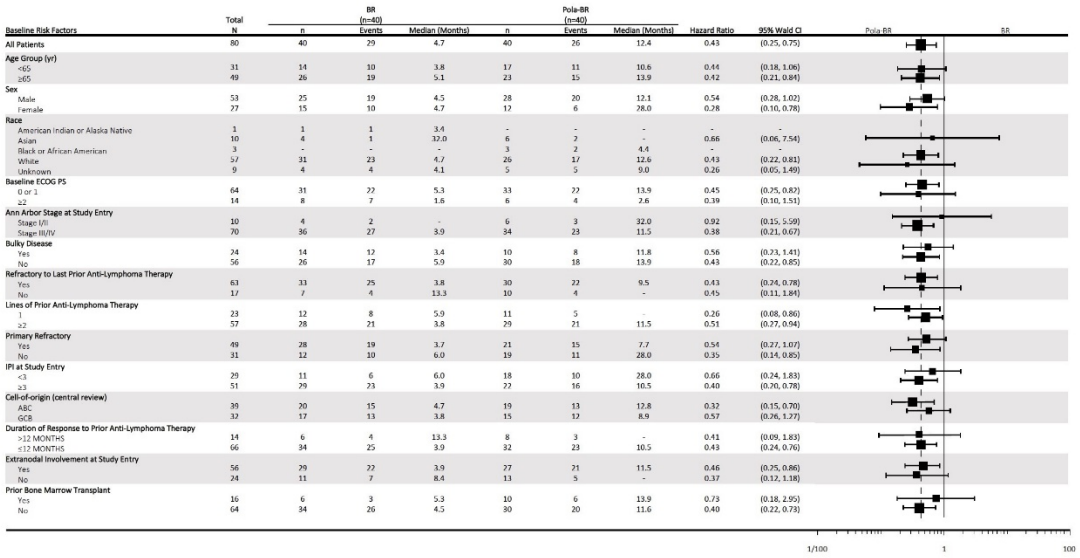



No.; number; Pola: Polivy; BR: bendamustine and rituximab; HR: hazard ratio. CI: confidence interval

## Results of subgroup analyses

Results of subgroup analysis of overall survival were consistent with the results seen in the overall DLBCL population (see Figure 3 below).

**Figure 3 Forest plot of Overall survival**




ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; ABC: activated B-cell; GCB: germinal center B-cell like; Pola: Polivy; BR: bendamustine and rituximab; CI: confidence interval

*Extension cohort (n=106)*

The median age was 70 years (range 24 to 94 years) 78% of patients were white and 49% were male. The majority of patients (94%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had ABC DLBCL and 40% of patients had GCB DLBCL. Primary reasons patients were not candidates for HSCT included age (44%), insufficient response to salvage therapy (29%) and prior transplant failure (14%). The median number of prior therapies was 2 (range: 1-7) with 35% (n=37) receiving one prior therapy, 26% (n=27) receiving 2 prior therapies, and 40% (n=42) receiving 3 or more prior therapies. 76% of patients had refractory disease.

**Table 5 Summary of efficacy in extension cohort with previously treated DLBCL from study GO29365**

| | **Polivy + bendamustine + rituximab n = 106** |
|---|---|
| | **Median observation time 9.7 months** |
| ***Primary Endpoint*** | |
| Complete Response Rate* (IRC-assessed) at End of treatment** | |
| Responders (%) [95% CI] | 42 (39.6) [30.3, 49.6] |
| ***Key Endpoints*** | |
| Overall Survival | |
| Number (%) of patients with event | 51 (48.1) |
| Median OS (95% CI), months | 11.0 (8.3, 14.2) |
| Progression Free survival (INV-assessed) | |
| Number (%) of patients with event | 68 (64.2) |
| Median PFS (95% CI), months | 5.5 (4.8, 6.9) |

| | |
|---|---|
| Duration of response (INV-assessed) | |
| Number of patients included in analysis | 66 (62.3) |
| Number (%) of patients with event | 28 (42.4) |
| Median DOR (95% CI), months | 5.9 (4.8, 11.6) |
| Overall Response Rate* (INV-assessed) at End of Treatment** | |
| Responders (%) (CR, PR) | 45 (42.5) [32.9, 52.4] |
| Complete Response (%) (CR) | 39 (36.8) |
| 95% CI Clopper-Pearson | [27.6, 46.7] |
| Partial Response (%) (PR) | 6 (5.7) |
| 95% CI Clopper-Pearson | [2.1 – 11.9] |
| Best Overall Response Rate* (INV-assessed) | |
| Responders (%) [CR, PR] 95% CI Clopper-Pearson | 66 (62.3) [52.3, 71.5] |
| Complete Response (%) [CR] | 52 (49.1) |
| 95% CI Clopper-Pearson | [39.2, 59.0] |
| Partial Response (%) [PR] | 14 (13.2%) |
| 95% CI Clopper-Pearson | [7.4, 21.2] |

IRC: Independent Review Committee; INV: Investigator; CI: Confidence Interval, HR: Hazard Ratio; CMH Cochran-Mantel-Haenszel; OS: Overall survival; NE: Not evaluable; PFS: progression free survival; DOR: Duration of response

*Per modified Lugano 2014 criteria: Bone marrow confirmation of PET-CT CR required. PET-CT PR required meeting both PET-CT criteria and CT criteria [56].

**6-8 weeks after day 1 of cycle 6 or last study treatment

*** Stratification by duration of response to prior therapy (≤12 months vs >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 (excluding extension cohort) 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 (± 233) ng/mL and the area under the concentration-time curve from time zero to infinity ($AUC_{inf}$) was 1860 (± 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 (± 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 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 3A4/5 but does not induce major CYP enzymes. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations.

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 of radioactivity is excreted in faeces and the minority 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 <65 years of age (n=187) and patients ≥65 years of age (n=273)

*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 normal renal function (CrCL ≥ 90 mL/min, n=185), based on a population pharmacokinetic 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 Polivy. 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 Polivy 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) and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

## *6.3 Shelf Life*

Unopened vial

The shelf life of the unopened vial is 2 years at 2°C to 8°C.

Stability of reconstituted solution in the vial

From a microbiological point of view, the reconstituted solution and prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

If the solution is not used immediately, refer to Section 6.6 for detailed instructions and storage times of the reconstituted drug product solution and prepared solution for infusion.

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

Refer to sections 6.3 and 6.6 for storage of the sterile product that has been reconstituted and diluted in infusion diluent.

### *6.5 Nature And Contents Of Container*

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

### *6.6 Special Precautions For Disposal and Other Handling*

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.

*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.

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 72 hours at 2 °C to 8 °C and up to 24 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.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Acceptable chemical and physical stability of the prepared solution for infusion has been demonstrated for the durations listed in Table 5. Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight .*

**Table 5 Durations for which acceptable chemical and physical stability of the prepared solution for infusion have been demonstrated**

| Diluent used to prepare solution for infusion | Solution for infusion storage conditions[1] |
|---|---|
| 0.9% Sodium Chloride | Up to 72 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 72 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) |

[1]To 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 24 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 5.

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

## 7. MEDICINE SCHEDULE

Prescription

## 8 SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

## 9 DATE OF FIRST APPROVAL

19th December 2019

## 10 DATE OF REVISION OF THE TEXT

27 July 2021

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| 6.6 | Extension of the shelf life of the polatuzumab vedotin finished product after dilution with 0.9% sodium chloride to 72 hours at 2°C-8°C |