PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Polivy 30 mg powder for concentrate for solution for infusion

Polivy 140 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: polatuzumab vedotin

Polivy 30 mg powder for concentrate for solution for infusion

Each vial of powder for concentrate for solution for infusion contains 30 mg of polatuzumab vedotin. After reconstitution, each mL contains 20 mg of polatuzumab vedotin.

Polivy 140 mg powder for concentrate for solution for infusion

Each vial of powder for concentrate for solution for infusion contains 140 mg of polatuzumab vedotin. After reconstitution, each mL contains 20 mg of polatuzumab vedotin.

Polatuzumab vedotin is an antibody-drug conjugate composed of the anti-mitotic agent monomethyl auristatin E (MMAE) covalently conjugated to a CD79b-directed monoclonal antibody (recombinant humanized immunoglobulin G1 [IgG1], produced in Chinese Hamster Ovary cells by recombinant DNA technology).

For the full list of excipients, see section 6.1

Contains sugar (sucrose) Polivy 30 mg – 77 mg & Polivy 140 mg – 309 mg

3. PHARMACEUTICAL FORM

Polivy is a powder for concentrate for solution for infusion (powder for concentrate). Polivy is a preservative-free white to grayish-white lyophilized cake supplied in single dose vials that delivers 30 mg or 140 mg of polatuzumab vedotin.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

4.2 Posology and method of administration

General

Substitution by any other biological medicinal product requires the consent of the professional medical practitioner.

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicine 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.

For information on rituximab, bendamustine, cyclophosphamide, doxorubicin, or prednisone, refer to their respective full professional professional information. Refer to Table 2 for dose modification recommendations for neutropenia and thrombocytopenia

Posology

Diffuse large B-cell lymphoma

Previously untreated patients:

The recommended dose of Polivy is 1,8 mg/kg given as an intravenous infusion every 21 days for 6 cycles in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP). Polivy, rituximab, cyclophosphamide, and doxorubicin can be administered in any order on Day 1 after the administration of prednisone. Prednisone is administered on Days 1–5 of each cycle. Cycles 7 and 8 consist of rituximab as monotherapy.

Relapsed or refractory patients

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.

Previously untreated and relapsed or refractory patients

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.

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.

There are different possible dose modifications for Polivy in patients with previously untreated DLBCL and those who are relapsed or refractory.

For dose modifications to manage peripheral neuropathy see Table 1

Table 1 Polivy dose modifications for Peripheral Neuropathy

Indication	**Severity on Day 1 of any cycle**	**Dose modification**
Previously untreated DLBCL	Grade 2[a]	Sensory neuropathy: ● Reduce Polivy to 1,4 mg/kg ● If Grade 2 persists or recurs at Day 1 of a future cycle, reduce Polivy to 1,0 mg/kg ● If already at 1,0 mg/kg and Grade 2 occurs at Day 1 of a future cycle, discontinue Polivy Motor neuropathy: ● Hold Polivy dosing until improvement to Grade ≤ 1. ● Restart Polivy at the next cycle at 1,4 mg/kg. ● If already at 1,4 mg/kg and Grade 2 occurs at Day 1 of a future cycle, withhold Polivy dosing until improvement to ≤ Grade 1. Restart Polivy at 1,0 mg/kg. ● If already at 1,0 mg/kg and Grade 2 occurs at Day 1 of future cycle, discontinue Polivy.

		If concurrent sensory and motor neuropathy occur, follow the most severe restriction recommendation above.
	Grade 3[a]	Sensory neuropathy: • Withhold Polivy dosing until improvement to Grade ≤ 2. • Reduce Polivy to 1,4 mg/kg. • If already at 1,4 mg/kg, reduce Polivy to 1,0 mg/kg. If already at 1,0 mg/kg, discontinue Polivy. Motor neuropathy: • Withhold Polivy dosing until improvement to Grade ≤ 1. • Restart Polivy at the next cycle at 1,4 mg/kg. • If already at 1,4 mg/kg and Grade 2–3 occurs, withhold Polivy dosing until improvement to Grade ≤ 1. Restart Polivy at 1,0 mg/kg. • If already at 1,0 mg/kg and Grade 2–3 occurs, discontinue Polivy. If concurrent sensory and motor neuropathy occur, follow the most severe restriction recommendation above.
	Grade 4	Discontinue Polivy.
R/R DLBCL	Grade 2-3	Withhold Polivy dosing until improvement to Grade ≤ 1. If recovered to Grade ≤1 on or before Day 14, restart Polivy at a permanently reduced dose of 1,4 mg/kg. If a prior dose reduction to 1,4 mg/kg has occurred, discontinue Polivy.If not recovered to Grade ≤1 on or before Day 14, discontinue Polivy.
	Grade 4	Discontinue Polivy.

[a] R-CHP may continue to be administered

For dose modifications to manage myelosuppression (*see Section 4.4*) see Table 2 below.

Table 2	**Polivy, chemotherapy, and rituximab dose modifications to myelosuppression**	
Indication	**Severity of myelosuppression on Day 1 of any cycle**	**Dose modification[a]**
Previously untreated DLBCL	Grade 3–4 Neutropenia	Withhold all treatment until ANC* recovers to > 1000/□L. If ANC recovers to > 1000/□L on or before Day 7 of the treatment cycle, resume all treatment without any additional dose reductions. If ANC recovers to > 1000/□L after Day 7: ● resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25–50 % ● if cyclophosphamide and/or doxorubicin are already reduced by 25 %, consider reducing one or both agents to 50 %
	Grade 3–4 Thrombocytopenia	Withhold all treatment until platelets recover to > 75,000/□L. If platelets recover to > 75,000/□L on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to > 75,000/□L after Day 7: ● resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25–50 % ● if cyclophosphamide and/or doxorubicin are already reduced by 25 %, consider reducing one or both agents to 50 %

R/R DLBCL	Grade 3-4 Neutropenia[1]	Withhold all treatment until ANC recovers to > 1000/ℓ L. If ANC recovers to > 1000/ℓ L on or before Day 7, resume all treatment without any additional dose reductions. If ANC recovers to > 1 000/ℓ L after Day 7: • 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
	Grade 3-4 Thrombocytopenia[1]	Withhold all treatment until platelets recover to > 75,000/□L. If platelets recover to > 75,000/□L on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to > 75,000/□L after Day 7: • 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

[1]If primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.
*ANC: absolute neutrophil count

For dose modifications to manage Infusion-related reactions (section 4.4) see Table 3 below.

Table 3 Polivy dose modifications for Infusion-related reactions (IRRs)

Indication	**Severity of IRR on Day 1 of any cycle**	**Dose modification**
Previously untreated and R/R DLBCL	Grade 1–3 IRR	Interrupt Polivy infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue Polivy. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Polivy. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. For the next cycle, infuse Polivy over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
	Grade 4 IRR	Stop Polivy infusion immediately. Give supportive treatment. Permanently discontinue Polivy.

Special Dosage Instructions

Pediatric use

The safety and efficacy of Polivy in children and adolescents less than 18 years have not been established.

Geriatric use

In patients with DLBCL (previously untreated and previously treated) no dose adjustment of Polivy is required in patients ≥ 65 years of age *(see Section 5.2 Pharmacokinetics in special populations)*. Clinical studies of Polivy did not include sufficient numbers of patients aged ≥ 65 years to determine whether they respond differently from younger patients.

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 of Polivy is required for patients with mild hepatic impairment [total bilirubin greater than ULN and less than or equal to 1,5 x ULN or aspartate transaminase (AST) greater than ULN] (*see Section 5.2 Pharmacokinetics in special populations*).

Method of administration

Polivy is for intravenous use.

The initial dose of Polivy should be administered as a 90-minute intravenous infusion. Patients should be monitored for IRRs/hypersensitivity 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.

Polivy must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. It 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 micrometer pore size) and catheter. Polivy must not be administered as intravenous push or bolus.
For instructions on reconstitution and dilution of the medicinal product before administration, see Section 6.6.

Precaution to be taken before handling or administering the product
Polivy contains a cytotoxic component which is covalently attached to the monoclonal antibody.
Follow applicable proper handling and disposal procedure (*see Section 6.6*).

4.3 Contraindications

Hypersensitivity to the polatuzumab vedotin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions

Traceability

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.

Sucrose

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrose-isomaltase insufficiency should not take Polivy.

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 *4.8 Undesirable Effects*). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with Polivy (see *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 *4.2 Posology and method of administration)*.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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 *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 *4.2 Posology 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 *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.

Human Immunodeficiency Virus (HIV)

Polivy has not been evaluated in patients with HIV. With regard to co-administration of CYP3A-inhibitors see section 4.5. Polivy has not been tested in patients with secondary immune deficiency due to HIV.

Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) testing and risks of Polivy

A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with Polivy. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent TB infection pose a risk for reactivation of tuberculosis and appropriate preventive therapy is indicated, regardless of HIV-status.

Diagnosis and treatment of latent infection, following national guidelines, should be initiated prior to use of Polivy. “People initiating Polivy treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with Polivy, and preventive treatment instituted if indicated.

Immunization

Live or live-attenuated vaccines should not be given concurrently with the treatment. Studies have

not been conducted in patients who recently received live vaccines.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported with Polivy treatment (see *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.

Infusion-related reactions

Polivy can cause IRRs, including severe cases. Delayed IRRs as late as 24 hours after receiving Polivy have occurred. An antihistamine and antipyretic should be administered prior to the administration of Polivy, and patients should be monitored closely throughout the infusion. If an IRR occurs, the infusion should be interrupted and appropriate medical management should be instituted (see section 4.2).

Embryo-Fetal Toxicity

Based on the mechanism of action and nonclinical studies, Polivy can harmful to the fetus when administered to a pregnant woman. 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 *Section 4.2 Special Dosage Instructions*, *Hepatic Impairment*).

4.5 Interaction with other medicines and other forms of interaction

No dedicated clinical interaction studies with Polivy in humans have been conducted.

Medicines interactions with co-medications that are CYP3A inhibitors, inducers or substrates and co-medications that are P-gp inhibitors.

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 medicines that are CYP3A substrates (e.g., midazolam).

Strong CYP3A4 inducers (e.g., rifampicin, carbamezapine, phenobarbital, phenytoin, St John's wort [Hypericum perforatum]) may decrease the exposure of unconjugated MMAE.

Medicine interactions of rituximab, bendamustine, cyclophosphamide, and doxorubicin in combination with polatuzumab vedotin.

The pharmacokinetics (PK) of rituximab, bendamustine, cyclophosphamide, and doxorubicin 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. The plasma AUC of acMMAE and unconjugated MMAE for Polivy plus R-CHP are in line with other studies of Polivy. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

4.6 Fertility, pregnancy and lactation

Fertility

Based on animal studies, Polivy may impair male reproductive function and fertility.

Contraception

Females

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.

Males

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.

Pregnancy

Polivy is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Polivy can cause foetal harm based on the animal studies and the medicine's mechanism of action (see Section *5.1 Mechanism of Action*).

Labor and Delivery

The safe use of Polivy during labor and delivery has not been established.

Lactation

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 medicines 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.

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 Warnings and Precautions* and *4.8 Undesirable Effects*).

4.8 Undesirable effects

a. Summary of the Safety Profile

The safety of Polivy has been evaluated in 435 patients in Study GO39942 (POLARIX).The adverse drug reactions (ADRs) described in this section were identified based on the following:

- during treatment and follow-up of previously untreated DLBCL patients from the pivotal clinical trial POLARIX (GO39942), who received Polivy plus R-CHP (n=435) or R CHOP (n=438). In the Polivy plus R-CHP group, 91,7 % of patients received 6 cycles of Polivy versus 88,5 % of patients who received 6 cycles of vincristine in the R-CHOP group.

In previously untreated DLBCL patients treated with Polivy plus R-CHP:

- The most frequently-reported (≥ 30 %) adverse drug reactions (ADRs) in patients treated with Polivy plus R-CHP for previously untreated DLBCL were neuropathy peripheral (52,9 %), nausea (41,6 %), neutropenia (38,4 %), and diarrhoea (30,8 %).
- Serious adverse reactions were reported in 24,1 % of Polivy plus R-CHP treated patients.
- The most common serious adverse reactions reported in ≥ 5 % of patients were febrile

neutropenia (10,6 %) and pneumonia (5,3 %).

- The ADRs leading to treatment regimen discontinuation in > 1 % of patients treated with Polivy plus R-CHP was pneumonia (1,1 %).

The safety of Polivy has been evaluated in 151 patients in Study GO29365. The 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), randomised patients (n=39), and extension cohort patients (n=106) who received Polivy in combination with bendamustine and rituximab (BR) compared to randomised patients (n=39) who received BR alone. Patients in the Polivy treatment arms received a median of 5 cycles of treatment while randomised patients in the comparator arm received a median of 3 cycles of treatment.

In previously treated DLBCL patients treated with Polivy plus BR:

- The most frequently reported (≥ 30 %) ADRs (all grades) in patients treated with Polivy plus BR in previously treated DLBCL were neutropenia (45,7 %), diarrhoea (35,8 %), nausea (33,1 %), thrombocytopenia (32,5 %), anaemia (31,8 %) and neuropathy peripheral (30,5 %).
- Serious adverse reactions were reported in 41,7 % of Polivy plus BR treated patients.
- The most common serious adverse reactions reported in ≥ ≥ 5 % of patients were: febrile neutropenia (10,6 %), sepsis (9,9 %), pneumonia (8,6 %) and pyrexia (7,9 %).
- The ADR leading to treatment regimen discontinuation in > 5 % of patients treated with Polivy plus BR was thrombocytopenia (7,9 %).

b. Tabulated list of adverse reactions

The ADRs in 586 patients treated with Polivy are presented in Table 4. The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency. The corresponding frequency

category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Table 4 ADRs are listed by MedDRA system organ class (SOC).

Table 4 Tabulated list of ADRs in patients treated with Polivy in clinical trials

Infections and infestations	
Very common	pneumonia[a], upper respiratory tract infection
Common	sepsis[a], herpes virus infection[a], cytomegalovirus infection, urinary tract infection[c]
Blood and lymphatic system disorders	
Very common	febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia
Common	lymphopenia, pancytopenia
Metabolism and nutrition disorders	
Very common	hypokalaemia, decreased appetite
Common	hypocalcaemia, hypoalbuminemia
Nervous system disorders	
Very common	neuropathy peripheral
Common	dizziness
Eye disorders	
Uncommon	vision blurred[b]
Respiratory, thoracic and mediastinal disorders	
Very common	cough

Common	pneumonitis, dyspnoea[c]
Gastrointestinal disorders	
Very common	diarrhoea, nausea, constipation, vomiting, mucositis[c], abdominal pain
Skin and subcutaneous tissue disorders	
Very common	alopecia[c]
Common	pruritus, skin infections[c], rash[c], dry skin[c]
Musculoskeletal disorders	
Common	arthralgia, myalgia[c]
General disorders and administration site conditions	
Very common	pyrexia, fatigue, asthenia
Common	peripheral edema[c], chills
Investigations	
Very common	weight decreased
Common	transaminases increased, lipase increase[b], hypophosphataemia
Injury, poisoning and procedural complications	
Very Common	infusion related reaction

[a] ADR associated with fatal outcome
[b] ADRs observed in relapsed or refractory DLBCL only.
[c] ADRs observed in previously untreated DLBCL only.
The listed ADRs were observed in both previously untreated DLBCL and relapsed or refractory DLBCL except where indicated with footnotes.
Rare and very rare ADRs: none

Description of selected adverse drug reactions from clinical trials

Myelosuppression

In a placebo-controlled study GO39942 (POLARIX), 0,5 % of patients in the Polivy plus R-CHP arm discontinued study treatment due to neutropenia. No patients discontinued study treatment in the R-CHOP arm due to neutropenia. Thrombocytopenia events led to discontinuation of study

treatment in 0,2 % of patients in the Polivy plus R-CHP arm compared to no patients in the R-CHOP arm. No patients discontinued treatment due to anaemia in either the Polivy plus R-CHP arm or R-CHOP arm.

In an open-label study GO29365, 4,0 % of patients in the Polivy plus BR arms 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. In the Polivy plus BR arms, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia were reported in 40,4 %, 25,8 %, and 12,6 % of patients, respectively.

Peripheral Neuropathy (PN)

In a placebo-controlled study GO39942 (POLARIX), in the Polivy plus R-CHP arm, Grade 1, 2, and 3 PN were reported in 39,1 %, 12,2 % and 1,6 % of patients, respectively. In the R-CHOP arm, Grade 1, 2 and 3 PN events were reported in 37,2 %, 15,5 % and 1,1 % of patients, respectively. No Grade 4-5 PN events were reported in either the Polivy plus R-CHP arm or R-CHOP arm. 0,7 % of patients discontinued study treatment in the Polivy plus R-CHP arm due to PN compared to 2,3 % in the R-CHOP arm. 4,6 % of patients in the Polivy plus R-CHP arm had study treatment dose reduction due to PN compared to 8,2 % in the R-CHOP arm. In the Polivy plus R-CHP arm, the median time to onset of first event of PN was 2,27 months compared to 1,87 months in the R-CHOP arm. PN events resolved in 57,8 % of patients in the Polivy plus R-CHP arm as of the clinical cut off date compared to 66,9 % in the R-CHOP arm. The median time to peripheral neuropathy

resolution was 4,04 months in the Polivy plus R-CHP arm compared to 4,6 months in the R-CHOP arm.

In an open-label study GO29365, in the Polivy plus BR arms, Grade 1 PN and Grade 2 PN were reported in 15,9 % and 12,6 % of patients, respectively. In the BR arm, Grade 1 and 2 PN events were reported in 2,6 % and 5,1 % of patients, respectively. One Grade 3 PN event was reported in the Polivy plus BR arms and no PN events were reported in the BR arm. No Grade 4-5 PN events were reported in either the Polivy plus BR arms or BR arm. 2,6 % of patients discontinued Polivy treatment due to PN and 2,0 % of patients had Polivy dose reduction due to PN. No patients in the BR arm discontinued treatment or had dose reductions due to PN. In the Polivy plus BR arms, the median time onset of first event of PN was 1,6 months, and 39,1 % of patients with PN events reported event resolution (see *4.4 Warnings and Precautions*).

Infections

In a placebo-controlled study GO39942 (POLARIX), infections, including pneumonia and other types of infections, were reported in 49,7 % of patients in the Polivy plus R-CHP arm and 42,7 % of patients in the R-CHOP arm. Grade 3-4 infections occurred in 14,0 % of patients in the Polivy plus R-CHP arm and 11,2 % of patients in the R-CHOP arm. In the Polivy plus R-CHP arm, serious infections were reported in 14,0 % of patients and fatal infections were reported in 1,1 % of patients. In the R-CHOP arm, serious infections were reported in 10,3 % of patients and fatal infections were reported in 1,4 % of patients. 7 patients (1,6 %) in the Polivy plus R-CHP arm discontinued treatment due to infection compared to 10 patients (2,3 %) in the R-CHOP arm.

In an open-label study GO29365, infections including pneumonia and other types of infections, were reported in 48,3 % of patients in the Polivy plus BR arms 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 %) in the BR arm (see section *4.4 Warnings and Precautions*).

Progressive Multifocal Leukoencephalopathy (PML)

In a placebo-controlled study GO39942 (POLARIX), no cases of PML were reported.

In an open-label study GO29365, 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 section 4.4 Warnings and Precautions)*.

Hepatic toxicity

In a placebo-controlled study GO39942 (POLARIX), hepatic toxicity was reported in 10,6 % of patients in the Polivy plus R-CHP arm and 7,3 % of patients in the R-CHOP arm. In the Polivy plus R-CHP arm, most events were Grade 1 - 2 (8,7 %); Grade 3 events were reported in 1,8 % of patients. There were no Grade 4 or 5 events. Serious hepatic toxicity events were reported in 1 patient (0,2 %) and were reversible.

In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible (*see section 4.4 Warnings and Precautions)*.

Gastrointestinal Toxicity

In a placebo-controlled study GO39942 (POLARIX), gastrointestinal toxicity events were reported in 76,1 % of patients in the Polivy plus R-CHP arm compared to 71,9 % of patients in the R-CHOP arm. Most events were Grade 1–2, and Grade ≥ 3 events were reported in 9,7 % of patients in the Polivy plus R-CHP arm compared to 8,2 % of patients in the R-CHOP arm. The most common gastrointestinal toxicity events were nausea and diarrhoea.

In an open-label study GO29365, gastrointestinal_toxicity events were reported in 72,8 % 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 arms compared to 12,9 % of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhea and nausea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Medicine Reaction Report Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents; other antineoplastic agents; monoclonal antibodies: ATC code: L01FX14

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 humanised 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 efficacy and safety

Previously untreated DLBCL

The efficacy of Polivy was evaluated in an international, multicenter, randomized double-blind, placebo-controlled study (POLARIX, GO39942) in 879 patients with previously untreated DLBCL.

Eligible patients were age 18–80, and had IPI score 2–5, and ECOG Performance Status 0–2. Histologies included DLBCL (not otherwise specified (NOS), activated B-cell (ABC), germinal center B-cell (GCB)), HGBL (NOS, double-hit, triple-hit), and other large B-cell lymphoma subtypes (EBV positive, T-cell rich/histiocyte rich). Patients did not have known CNS lymphoma or peripheral neuropathy > Grade 1.

Patients were randomized 1:1 to receive Polivy plus R-CHP or R-CHOP for six 21-day cycles followed by two additional cycles of rituximab alone in both arms. Patients were stratified by IPI score (2 vs 3-5), presence or absence of bulky disease (lesion ≥ 7,5 cm), and geographical region.

Polivy was administered intravenously at 1,8 mg/kg on Day 1 of Cycles 1–6. R-CHP or R-CHOP were administered starting on Day 1 of Cycles 1–6 followed by rituximab alone on Day 1 of Cycles 7–8. Dosing in each treatment arm was administered according to the following:

- Polivy + R-CHP arm: Polivy 1,8 mg/kg, rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and prednisone 100 mg/day, on Days 1-5 of every cycle, orally.
- R-CHOP arm: rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1,4 mg/m², and prednisone 100 mg/day, on Days 1-5 of every cycle, orally.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. The median age was 65 years (range 19 to 80 years), 53,6 % of patients were white and 53,8 % were male, 43,8 % had bulky disease, 38,0 % had IPI score 2, 62,0 % had

IPI score 3–5, and 88,7 % had Stage 3 or 4 disease. The majority of patients (84,2 %) had DLBCL (including NOS, ABC, and GCB).

211 patients did not have a cell of origin (COO) result reported. Of the COO evaluable population (n=668), 33,1 % of patients had ABC like DLBCL and 52,7 % of patients had GCB like DLBCL, by gene expression profiling.

The primary endpoint of the study was investigator-assessed progression free survival. The median duration of follow up was 28,2 months. Efficacy results are summarized in Table 5 and in Figure 1.

Table 5 Summary of efficacy in patients with previously untreated DLBCL from Study GO39942 (POLARIX)

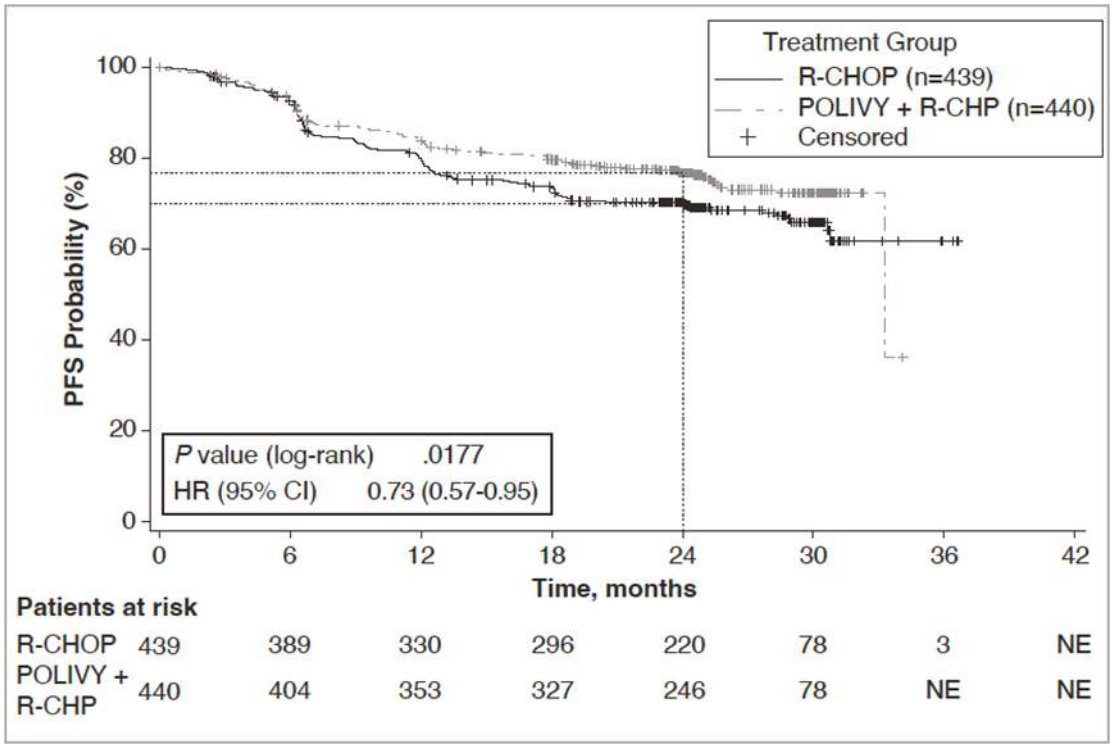
	Polivy + R-CHP N=440	**R-CHOP N=439**
Primary Endpoint		
Progression free survival[1,*]		
Number (%) of patients with events	107 (24,3 %)	134 (30,5 %)
HR (95 % CI)	0,73 [0,57, 0,95]	
p-value[3,**]	0,0177	
2-year PFS estimate (%)	76,7	70,2
[95 % CI]	[72,65, 80,76]	[65,80, 74,61]
Key secondary endpoints		
Event-free survival (EFS_{eff})[1]		
Number (%) of patients with event	112 (25,5 %)	138 (31,4 %)
HR [95 % CI]	0,75 [0,58, 0,96]	
p-value[3,**]	0,0244	
Objective Response Rate (ORR) at End of Treatment[2]		

Responders (%) (CR, PR)	376 (85,5 %)	368 (83,8 %)
Difference in response rate (%) [95 % CI]	1,63 [-3,32, 6,57]	
Complete Response (%) (CR) Rate[2,*]		
Responders (%)	343 (78,0 %)	325 (74,0 %)
Difference in response rate (%) [95 % CI]	3,92 [-1,89, 9,70]	
Partial response (%) (PR)	33 (7,5 %)	43 (9,8 %)
95 % CI Clopper-Pearson	[5,22, 10,37]	[7,18, 12,97]

INV: Investigator; BICR: Blinded independent central review; CI: Confidence interval; HR: Hazard ratio; PFS: Progression free survival; EFSeff: Event free survival efficacy: used to reflect EFS events that are due to efficacy and defined as time from date of randomization to the earliest occurrence of any of the following: disease progression/relapse, death due to any cause, the primary efficacy reason determined by the investigator, other than disease progression/relapse, that led to initiation of any non-protocol specified anti-lymphoma treatment (NALT), if biopsy was obtained after treatment completion and was positive for residual disease regardless of whether NALT was initiated or not; CMH: Cochran-Mantel-Haenszel
1) INV-assessed
2) BICR-assessed
3) Log-rank test, stratified
*Per Lugano 2014 Response Criteria
**Stratified by IPI (2 vs 3-5), presence or absence of bulky disease, geography

At the interim analysis, the key secondary endpoint of OS was immature and was not statistically different [stratified hazard ratio of 0,94 (95 % CI, 0,65, 1,37); p=0,7524].

Figure 1 Kaplan Meier curve of INV-assessed progression-free survival (PFS) in Study GO39942 (POLARIX)



Relapsed or refractory DLBCL

The efficacy of Polivy was evaluated in an international, multicenter, open-label study (GO29365) which included a randomised cohort of 80 patients with previously treated DLBCL. Patients were randomized 1:1 to receive Polivy plus BR or BR alone for six 21-day cycles. Patients were stratified by duration of response to last prior treatment of ≤ 12 months or > 12 months.

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 indolent lymphoma (FL), grade 3b FL, significant cardiovascular or pulmonary disease, active infections, AST or alanine transaminase (ALT) > 2,5 x ULN or total bilirubin ≥ 1,5 x ULN, creatinine > 1,5 x ULN (or CrCl < 40 mL/min) unless due to underlying lymphoma.

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.

Among the 80 patients who were randomized to receive Polivy plus BR (n=40) or BR alone (n=40) the majority were white (71 %) and male (66 %). The median age was 69 years (range: 30-86 years). Sixty-four out of 80 patients (80 %) had ECOG performance status (PS) of 0-1 and 14 out of 80 patients (18 %) had ECOG PS of 2. The majority of patients (98 %) had DLBCL not otherwise specified (NOS). Overall, 48 % of patients had activated B-cell (ABC) DLBCL and 40 % 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. All except one patient in the pola+BR arm of the randomized Phase II were naïve to bendamustine treatment. 80 % of patients had refractory disease. For patients who received polatuzumab vedotin plus BR and had CD3+ lymphocyte count evaluated, the absolute CD3+ lymphocyte count was > 200 cells/µL in 95 %, 79 % and 83 % of patients analyzed at prior to therapy (n=134), end of treatment (n=72) and 6 months after end of treatment (n=18), respectively. 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 PET-CT by an independent review committee (IRC).

Table 6 Summary of efficacy in randomized 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 secondary and exploratory Endpoints		
Duration of response (INV-assessed)		
Number of patients included in analysis	28	13
Number (%) of patients with event	17 (60,7)	11 (84,6)
Median DOR (95 % CI), months	10,3(5,6, NE)	4,1 (2,6, 12,7)
HR [95 % CI]	0,44 [0,20, 0,95]	
p-value (Log-Rank test, stratified***)	0,0321	
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]

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

Overall survival (OS) was an exploratory endpoint which was not type 1 error controlled. The median OS in the Polivy plus BR arm was 12,4 months (95 % CI: 9,0, NE) vs 4,7 months (95 % CI: 3,7, 8,3) in the control arm. The unadjusted estimate for OS HR was 0,42. When accounting for the influence of baseline covariates the OS HR was adjusted to 0,59. Covariates included primary refractory status, number of prior lines of therapy, IPI, and prior stem cell transplant.

Investigator-assessed progression free survival (PFS) was an exploratory endpoint which was not type 1 error controlled. The median PFS in the Polivy plus BR arm was 7,6 months (95 % CI: 6,0, 17,0) vs 2,0 months (95 % CI: 1,5, 3,7) in the control arm. The unadjusted estimate for PFS HR was 0,34.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. In Studies GO39442 (POLARIX) and GO29365, 1,4 % (6/427) and 5,2 % (12/233) of patients tested positive for antibodies against polatuzumab vedotin positive for neutralising antibodies. 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.

Based on population PK analysis, the predicted acMMAE concentration at the end of Cycle 6 is approximately 80 % of the theoretical steady-state value. 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. 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.

Based on population pharmacokinetics simulations, a post-hoc analysis predicted exposure to unconjugated MMAE for patients with bodyweight over 100 kg to be increased by not more than 55 %.

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/Biotransformation

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.

Elimination

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

Paediatric Population

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

Geriatric Population

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on ~~a~~ population PK analyses with patients aged 19-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients <65 years of age (n=394) and patients ≥65 years of age (n=495) based on population PK analyses.

Renal impairment

In patients with mild (CrCL 60-89 mL/min, n=361) or moderate (CrCL 30-59 mL/min, n=163) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with normal renal function (CrCL ≥ 90 mL/min, n=356), based on a population pharmacokinetic analysis. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 mL/min, n=4) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis *(see 4.2 Posology 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=133], acMMAE exposures are similar whereas unconjugated MMAE AUC are not more than 40 % higher compared to patients with normal hepatic function (n=737), based on a population pharmacokinetic analyses.

There are insufficient data to assess the impact of moderate hepatic impairment (total bilirubin > 1,5 – 3 × ULN, n= 11) on PK. Limited data are available in patients with severe hepatic impairment or liver transplantation (see *4.2 Posology and method of administration)*.

5.3 Preclinical safety data

Genotoxicity

No dedicated mutagenicity studies have been performed with polatuzumab vedotin. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

MMAE was genotoxic in the rat bone marrow micronucleus study probably through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent.

Carcinogenicity

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

Impairment of fertility

No dedicated fertility studies in animals have been performed with polatuzumab vedotin. However, results of the 4-week rat toxicity study indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. Testicular seminiferous tubule degeneration did not reverse following a 6-week treatment-free period and correlated with decreased testes weight and gross findings at recovery necropsy of small and/or soft testes in males given $\geq$ 2 mg/kg.

Reproductive toxicity

No dedicated teratogenicity studies in animals have been performed with polatuzumab vedotin. However, treatment of pregnant rats with MMAE at 0,2 mg/kg caused embryolethality and foetal malformations (including protruding tongue, malrotated limbs, gastroschisis, and agnathia). Systemic exposure (AUC) in rats at a dose of 0,2 mg/kg MMAE is approximately 50 % of the AUC in patients who received the recommended dose of 1,8 mg/kg Polivy every 21 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20 (E 432)

Sodium hydroxide (for pH-adjustment)

Succinic acid

Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vials

30 months

Reconstituted solution

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).

Diluted solution

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 refrigerated (2 °C - 8 °C), unless dilution has taken place in controlled and validated aseptic conditions. Chemical and physical stability of

the prepared solution for infusion has been demonstrated for the durations listed in Table 7. The diluted solution must be discarded if storage time exceeds the limits specified in Table 7.

Table 7 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 % Glucose	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.

This medicine should not be used after the expiry date (“EXP” for the powder, and “Discard After” for the constituted oral solution) on the carton and on the bottle.

6.4 Special precautions for storage

Vials

Store unopened vials at 2 °C – 8 °C.

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

Do not freeze. Do not shake.

Shelf life of reconstituted product and solution for infusion

The reconstituted solution and solution for infusion should not be frozen or exposed to direct

sunlight.

6.5 Nature and contents of container

Polivy 30 mg powder for concentrate for solution for infusion:

6 mL vial (colourless Type 1 glass) closed with a stopper (fluororesin laminate), with an aluminium seal with plastic flip-off cap containing 30 mg polatuzumab vedotin.

Pack size of one vial.

Polivy 140 mg powder for concentrate for solution for infusion:

20 mL vial (colourless Type 1 glass) closed with a stopper (fluororesin laminate), with an aluminium seal with plastic flip-off cap containing 140 mg polatuzumab vedotin.

Pack size of one vial.

6.6 Special Instructions for Use, Handling and Disposal

Polivy contains a cytotoxic component. To be administered under the supervision of a physician experienced in the use of cytotoxic agents. Procedures for proper handling and disposal of antineoplastic and cytotoxic medicines should be used.

The reconstituted product contains no preservative and is intended for single-dose only. Proper aseptic technique throughout the handling of this medicinal product should be followed.

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.

Reconstitution

1. Polivy 30 mg: Using a sterile syringe, slowly inject 1,8 mL of sterile water for injection into the 30 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. Polivy 140 mg: 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.
3. Swirl the vial gently until completely dissolved. Do not shake
4. 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.

Instructions for 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 50 mL 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:

$$\text{Volume} = \frac{\text{Polivy dose (1,8 or 1,4 mg/kg) X patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/mL)}}$$

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.

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 7 (see section 6.3).

Polivy must be administered using a dedicated infusion line equipped with sterile, non-pyrogenic, low protein binding in-line or add-on filter (0,2 or 0,22 micrometer pore size) and catheter.

Polivy is compatible with intravenous infusion bags with product contacting materials of polyvinyl chloride (PVC) or polyolefins such as polyethylene (PE) and polypropylene. In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane, polybutadiene, acrylonitrile butadiene styrene, polycarbonate, polyetherurethane, fluorinated ethylene propylene, or polytetrafluorethylene and with filter membranes composed of polyether sulfone or polysulfone.

Disposal of unused/expired medicines

Polivy is for single-use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER

Polivy 30 mg: 56/26/0149

Polivy 140 mg : 56/26/0150

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 28 November 2023

10. DATE OF REVISION OF THE TEXT

Last revision: 14 November 2023

Approved Manufacturer(s):

BSP Pharmaceuticals S.p.A. Via Appia Km 65.561

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Italy