Date: 19 August 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Polivy

International non-proprietary name: polatuzumab vedotin
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strengths: 30 mg, 140 mg
Route(s) of administration: intravenous
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 67165
Decision and Decision date: approved on 15 June 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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Table of contents

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1 Terms, Definitions, Abbreviations

acMMAE	Antibody-conjugated monomethyl auristatin E
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BR	Bendamustine plus rituximab
BWT	Body weight
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
Cmax	Maximum observed plasma/serum concentration of drug
CLNS	Non-specific linear clearance
CNS	Central nervous system
CYP	Cytochrome P450
DLBCL	Diffuse large B-cell lymphoma
DLT	Drug limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
FL	Follicular lymphoma
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
IC_{50}	Half-maximal inhibitory concentration
Ig	Immunoglobulin
INN	International Nonproprietary Name
ITT	Intention to treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MMAE	Monomethyl auristatin E
N/A	Not applicable
NHL	Non-Hodgkin's B-cell lymphoma
NO(A)EL	No Observed (Adverse) Effect Level
PBPK	Physiology-based PK
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
POLA	Complete ADC
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
PV	Polatuzumab vedotin
RBC	Red blood cells
RMP	Risk Management Plan
R/R	Relapsed/Refractory
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)

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TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance polatuzumab vedotin of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 12 June 2018.

2.2 Indication and Dosage

2.2.1 Requested Indication

Polatuzumab vedotin in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. Polivy, bendamustine and rituximab can be administered in any order on Day 1 of each cycle. When administered with Polivy, the recommended dose of bendamustine is 90 mg/m^2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m^2 on Day 1 of each cycle.
If not already premedicated, premedication with an antihistamine and anti-pyretic should be administered to patients prior to 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.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	14 August 2020
Formal control completed	20 August 2020
List of Questions (LoQ)	26 November 2020
Answers to LoQ	25 January 2021
Predecision	22 April 2021
Answers to Predecision	10 May 2021
Final Decision	15 June 2021
Decision	approval

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3 Medical Context

Diffuse large B cell lymphomas (DLBCL) represent approximately 1/3 of all non-Hodgkin lymphomas (NHL) and consist of a group of aggressive mature B-cell malignancies, defined in the most recent WHO 2016 classification by site of origin, histology, immune-phenotype and genetic profiling/gene expression. The aetiology is unknown but risk factors, including HIV infection, have been identified. Incidence of all NHL in Switzerland (2011-2015) was calculated as age standardised rates (ASR) per 100,000 person years of 21 for men and 12 for women. Prevalence of NHL in Switzerland in 2014 was about 8,800 cases (men and women together) [http://www.nicer.org, Statistics NHL].
For nearly two decades, the standard first-line therapy for the majority of DLBCL cases has been 6 – 8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), irrespective of prognostic subtype. All stage 5-year survival rates range from 60% to 70%, and 10-year PFS is about 35% and OS about 40-50%.
Approximately 50% of patients will relapse, and their prognosis is dependent on various factors, including time since last therapy (</≥12 months), international prognostic index (IPI), bulky disease, number of extranodal sites and previous rituximab therapy. About 50% of these patients have chemo-sensitive relapse and can be cured with salvage therapy followed by high-dose chemotherapy and autologous haematopoietic stem cell transplantation (HSCT).
Patients who (e.g. because of age, comorbidities, ECOG etc.) are not eligible for intensive treatment including autologous HSCT have a dismal prognosis and will ultimately die of their relapsed disease. There is no universally accepted standard regimen in this setting. In the largest retrospective analysis to date, including four refractory DLBCL datasets, the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. At 2 years, the OS fraction was 20% [Crump et al, Blood 2017].
More recently, CAR-T cell products have been approved for DLBCL, showing complete response rates between 24% and 55% and median OS rates between 8.2 and 17.4 months in patients who had received more than two prior lines of therapy. This procedure involves intensive treatment as well as complex logistics. In addition, a range of novel combination therapies have been tested and are used in relapsed/refractory settings in later lines following relapse after autologous HSCT. However, none of these has yet been approved for patients having received more than two prior lines of treatment, and there is a need for better tolerated and/or more effective therapies, especially for patients with relapsed DLBCL who are not eligible for autologous HSCT, CAR-T cell therapy or, in selected cases, allogeneic HSCT.

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4 Quality Aspects

4.1 Drug Substance

Polatuzumab vedotin is an antibody-drug conjugate composed of an anti-mitotic agent, monomethyl auristatin E (MMAE), covalently conjugated to a CD79b-directed monoclonal antibody (IgG1κ). CD79b is a component of the B-cell receptor (not found on plasma cells). Rapid internalisation of the antibody-drug conjugate (ADC) enables targeted delivery of the cytotoxic agent to B cells.
The drug substance antibody intermediate polatuzumab is expressed in a CHO (Chinese hamster ovary) host cell line. Polatuzumab consists of two identical light chain polypeptides and two identical heavy chain polypeptides linked with intra- and inter-chain disulfide bonds. Both heavy chains contain one oligosaccharide chain in the conserved Fc site (Asn297). Polatuzumab is produced using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps.
The antibody intermediate and its impurities were characterised using state of the art methods. The specifications for the antibody intermediate include e.g. identity tests, impurity tests and a potency assay. The antibody intermediate and the linker-drug intermediate (vcMMAE) are conjugated to form the drug substance polatuzumab vedotin at Lonza Ltd., Visp, Switzerland. The synthesis of the linker-drug intermediate consists of a convergent, solution phase, fragment-based peptide synthesis consisting of six separate stages.

The characterisation of the antibody-drug conjugate and its impurities were performed using state of the art methods e.g. ESI-TOF-MS, LC-MS/MS, HIC and chromatographic methods for detection of charge and size variants. The specifications include e.g. identity tests, impurity tests, a cell-based potency assay and a potency by binding assay. The intact molecular weight for polatuzumab vedotin is 149.6 kDa (without N-linked glycosylation).
Drug substance batch analysis data from 26 commercial scale batches from the current manufacturing site are provided. Additional batch data for the drug substance used in nonclinical studies and clinical trials are presented, and their comparability has been demonstrated. All the analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines.
The drug substance is stored at -20°C. No significant changes are observed within the proposed storage conditions. A shelf life of 36 months has been accepted.

4.2 Drug Product

The finished product is available as 140 mg or 30 mg lyophilised product in 20 mL and 6 mL vials, respectively. It is intended for intravenous infusion after reconstitution with sterile water for injection (SWFI) and dilution in sodium chloride solution or dextrose solution. The reconstituted polatuzumab vedotin is formulated in an aqueous buffered solution, at pH 5.3, containing sucrose and polysorbate 80. All excipients comply with the European Pharmacopoeia.
The finished product manufacturing process consists of thawing, optional pooling and mixing, sterile filtration, filling, lyophilisation, stoppering, capping/crimping and inspection steps, and is conducted at F. Hoffmann-La Roche AG, Kaiseraugst, Switzerland, (30 mg) and BSP Pharmaceuticals S.p.A., Latina Scalo, Italy (140 mg). Process validation studies were executed at commercial scale using three validation batches.
The specifications include relevant tests and limits, e.g. for appearance, colour, clarity, identity, cell-based potency assay, potency by binding assay, pH, reconstitution time, osmolality, purity and impurity tests (SE-UHPLC, iCIEF, RP-HPLC, HIC-HPLC), protein concentration by UV, particles, sterility and bacterial endotoxins. All non-compendial methods are validated in accordance with ICH guidelines.
Batch analysis data from 6 batches of 30 mg/vial and 10 batches of 140 mg/vial from the commercial site are provided. The container closure systems in contact with the finished product consist of a

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glass vial with laminated rubber stopper. The drug product is stored at 2 – 8°C, protected from light. A shelf life of 30 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of drug substance and drug product is supported by data from studies with recommended storage conditions, as well as accelerated and stress studies. Safety aspects with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

The applicant provided a nonclinical study package that is in accordance with the ICH S9 guideline. Pivotal safety pharmacology and toxicology studies with polatuzumab vedotin or its surrogate antibody were conducted in compliance with Good Laboratory Practice (GLP).

Pharmacology

In vitro studies showed that polatuzumab binds only to the human B cell subpopulation of peripheral blood mononuclear cells (PBMCs), but not to those of monkey, mouse, and rat. Therefore, a surrogate cynomolgus monkey antibody was developed that binds to the cynomolgus monkey B cell subpopulation without cross-reactivity to other species. Monomethyl auristatin E (MMAE)-conjugated and unconjugated monkey or human anti-CD79b antibodies bound with similarly high affinity to their target (1.21-1.83 nM), confirming that the process of cytotoxic drug conjugation did not influence respective target binding. Specificity of polatuzumab vedotin was determined in cellular assays. Polatuzumab vedotin dose-dependently inhibited proliferation of human CD79b-positive Ramos cell line (B cells Burkitt's lymphoma; IC_{50}=0.071 ± 0.014 nM) but not the Jurkat cell line (T cell line), indicating that cytotoxic activity is driven by intracellular release of MMAE after binding and internalisation to the target cells. Conjugation of MMAE cytotoxic drug does not compromise binding via the Fc part of the molecule, as shown in FcγR binding assays. *In vitro*, conjugated and unconjugated polatuzumab was able to induce moderate antibody-dependent cellular cytotoxicity (ADCC) activity, but had no complement-dependent cytotoxicity (CDC) activity. Moderate elevation of interleukin (IL) 1α and IP-10 was observed in the cytokine release assay.

In vivo antitumour activity of polatuzumab vedotin as a single agent or in combination with anti-CD20 antibodies or chemotherapy was studied in various immunodeficient mice mouse xenograft tumour models derived from human B-cell lymphoma cell lines (Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL) and Mantle cell lymphoma). Efficacy was preferentially shown in the combination therapy, which supports the proposed clinical indication. Pharmacological activity of surrogate antibody or surrogate antibody drug conjugate (ADC) was proven in single- and repeat-dose toxicity studies in cynomolgus monkeys. Surrogate ADC induced dose-dependent decreases in the B cell population (up to 85%) and the number of proliferating $CD20^+$ $Ki\text{-}67^+$ cells. Surrogate antibody alone also induced B cell depletion, but had no influence on cell proliferation. There were no alterations in total T cells ($CD3^+$), T-helper cells or cytotoxic T cells, or natural killer (NK) cells ($CD3^-/CD20^-$). The potential cross-reactivity of polatuzumab vedotin was evaluated with human tissue. Specific staining was observed in tissues with reported CD79b expression and correlated with the target organs of toxicity.

With regard to safety pharmacology, MMAE significantly inhibited hERG at very high concentration (IC_{50} > 100 µM), providing safety margin of >10 000 considering MMAE C_{max} measured in patients receiving 1.8 mg/kg polatuzumab vedotin (ca 10 nM; 7 ng/mL). No changes in body temperature, heart rate, blood pressure or electrocardiogram were observed in telemetered cynomolgus monkeys. There were no MMAE-related respiratory observations or effects on CNS either in rats or in monkeys across toxicology studies.

Pharmacokinetics

Pharmacokinetic studies were conducted in immunodeficient mice and cynomolgus monkeys. Toxicokinetics was studied in the repeat-dose studies in rats and cynomolgus monkeys.

The pharmacokinetic profile of polatuzumab vedotin is largely driven by the antibody part of the molecule and characterised by rapid absorption and distribution followed by a long elimination phase. The distribution of radiolabelled polatuzumab vedotin or antibody alone was fast, as shown in a study in female Sprague-Dawley rats. The highest radioactivity level was achieved 1 hour post-dose in highly perfused tissues, including liver, lungs, heart, kidneys, spleen, adrenal gland, ovaries, and bone marrow. In other tissues, the levels peaked 1 day post-dose. Little radioactivity was detected in brain and nerves over the entire study period. MMAE alone showed a rapid distribution to various tissues, particularly to highly perfused tissues such as liver, lungs, and kidneys.

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MMAE partitioned into the red blood cells (RBC) of mice, rats, and cynomolgus monkeys, but not into human RBC. The mean plasma protein binding of MMAE was 87.5%-90.8% bound in rats, 61.4%-69.2% bound in monkeys, and 70.6%-76.7% bound in humans.
MMAE was rapidly cleared from the plasma and was detected in bile within an hour post-dose in rats. Therefore, MMAE does not appear to undergo extensive metabolism *in vivo*. No human-specific metabolites were detected *in vitro*. MMAE is a substrate for CYP3A4/5.
The major route of elimination in nonclinical species dosed with radiolabelled polatuzumab vedotin was biliary/faecal and, to a lesser extent, urine, as in humans.

Toxicology
Toxicity evaluation included studies conducted with MMAE alone and/or polatuzumab vedotin in rats and cynomolgus monkeys to characterise off-target toxicities, and studies with the surrogate ADC in cynomolgus monkeys to evaluate pharmacologically induced toxicities.
Pivotal repeat-dose studies were conducted for up to 4 and 13 weeks in rats and cynomolgus monkeys, respectively. Rats were dosed once weekly and monkeys once every three weeks, which corresponds to the clinical dose regimen. Both dosing regimens ensured adequate exposure. The main target organs were bone marrow and lymphoid tissues mainly driven by MMAE and largely independent of target binding. Reversible bone marrow toxicity was associated with decreased white blood cell (WBC) and RBC parameters. The bone marrow hypocellularity led to increased susceptibility to infections. These findings correlate with neutropenia, thrombocytopenia and anaemia identified in clinical studies. Reversible lymphoid organ toxicity, characterised by thymus atrophy and necrosis, and spleen and rectal GALT (gut-associated lymphoid tissue) necrosis, correlate with the decreased peripheral lymphocytes. Additional toxicities found only in rat, but not in cynomolgus monkeys, included liver and testes toxicity. Liver is a recognised toxicity target organ in humans. Testes toxicity was characterised by seminiferous tubular degeneration and decreased spermatocytes. Findings in testis were not reversible and are in accordance with the genotoxic potential of MMAE as shown in the *in vivo* micronucleus test. The exposure (AUC) of animals was below the clinical exposure. A recommendation for sperm freezing is included in the information for healthcare professionals. No carcinogenicity studies were conducted, which is in line with ICH S9.
MMAE was embryotoxic and teratogenic in rats at exposures below the therapeutic exposure in patients. This is described in the information for healthcare professionals, and there is an appropriate recommendation in the Lactation/Pregnancy section. As MMAE does not absorb sunlight, no phototoxicity study is warranted according to ICH S10.
The toxicological findings, as well as their relevance for humans, are adequately described in the RMP. A PIP was submitted, and no nonclinical or clinical studies are currently planned.
According to the submitted ERA, polatuzumab vedotin does not represent a risk for the environment.

Conclusion

Overall, the submitted nonclinical documentation is considered to be sufficient to support the approval of Polivy, with the new active substance polatuzumab vedotin, in the proposed indication. The pharmacological and toxicological profile of Polivy is well characterised. The toxicity of Polivy is mainly triggered by the pharmacology. All nonclinical data that are relevant for safety are adequately included in the information for healthcare professionals

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6 Clinical and Clinical Pharmacology Aspects

6.1 Drug substance, Drug target and Mechanism of action

Polatuzumab vedotin (PV, Polivy®) is a CD79b targeted antibody-drug conjugate (ADC) that consists of a microtubule destabilising cytotoxic drug, monomethyl auristatin-E (MMAE), covalently conjugated to a humanised IgG1 anti-CD79b monoclonal antibody (MCDS4409A) through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl.
Polatuzumab vedotin has an average of 3.5 linked MMAE moieties per antibody (drug-to-antibody ratio, (DAR) = 3.5).

CD79b or Ig-β is part of the B-cell receptor. CD79b and CD79a (Ig-β and Ig-α) non-covalently associate with surface immunoglobulin (IgG, IgM, IgD, IgA or IgE) forming the B-cell receptor complex on B cells. Surface immunoglobulin thereby acts as an antigen binding site, and the transmembrane Ig-α/Ig-β heterodimer acts as a signalling domain via intracellular immunoreceptor tyrosine-based activation motifs (ITAM). Antigen binding induces ITAM phosphorylation and subsequent recruitment of multiple downstream kinases including SYK, LYN, SFK, SRC and BLK.

6.2 Clinical Pharmacology

The majority of the pharmacokinetic data summarised below was based on a pop PK analysis.
The range of the continuous covariate values in the pop PK dataset was sufficiently wide and in most cases there was a sufficient number of patients per category available to allow conclusions to be drawn on the impact of covariates on antibody-conjugated MMAE (acMMAE) and MMAE PK. However, the dataset included only 5 patients with moderate hepatic impairment and no patients with severe hepatic or renal impairment. Furthermore, most patients received 1.8 mg/kg or 2.4 mg/kg. Only very few patients received lower doses.
The integrated acMMAE-MMAE model fitted the PK profiles of acMMAE and unconjugated MMAE simultaneously. The structural model for acMMAE consisted of a two-compartment model with parallel linear and Michaelis-Menten elimination. Linear clearance consisted of two components: non-specific clearance declining with time (CLNS), and clearance exponentially-declining with time (CLt).
The final integrated model described the acMMAE and MMAE PK profiles reasonably well.

ADME

Biopharmaceutical Development
The majority of the POLA (complete ADC) clinical efficacy and safety studies were conducted with a liquid formulation, which had a considerably different composition than the commercial lyophilised formulation. Furthermore, the production processes were different.
To evaluate the bioavailability of the lyophilised formulation relative to the liquid formulation, the final pop PK model was applied to 103 patients receiving the lyophilised formulation. The “reference treatment” was represented by a historical dataset including 460 patients receiving the liquid formulation. Of these patients, 44 received POLA in combination with bendamustine and rituximab.

The pop PK model described the data after administration of the lyophilised formulation reasonably well.
Using all 460 patients receiving the liquid formulation as reference, formal bioequivalence was demonstrated for acMMAE and unconjugated MMAE Cmax, AUC and Ctrough.
Using the 44 patients receiving the liquid formulation plus bendamustine and rituximab as reference, formal bioequivalence was demonstrated for all acMMAE and unconjugated MMAE PK parameters except MMAE Ctrough, where the lower limit of the 90% CI was 0.785.
In summary, bioequivalence of the lyophilised and the liquid formulation was demonstrated.

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The maximum serum/plasma concentrations of total antibody or acMMAE were generally reached at the end of the i.v. infusion. Tmax of MMAE (2 to 3.4 days) was driven by its release from the antibody.

Pharmacokinetics after multiple Dosing

Based on population PK simulations of exposures for each cycle up to 6 cycles of 1.8 mg/kg Q3W dose, the acMMAE AUC and Ctrough at Cycle 6 values were approximately 1.4- and 2.2-fold of the values at Cycle 1. There were no apparent increases in Cmax values.

Based on PopPK simulations of 1.8 mg/kg Q3W for up to 30 treatment cycles, acMMAE was expected to reach its steady state after 15 cycles. Cycle 6 acMMAE AUC, Cmax and Ctrough values were 90%, 99%, and 80% of the model estimated steady-state AUC, Cmax and Ctrough values.

There was no accumulation of unconjugated MMAE after repeated dosing. Based on the population PK simulations of MMAE exposures for each cycle up to 6 cycles of 1.8 mg/kg Q3W dose, AUC and Cmax values were the highest in Cycle 1 after which they declined. The unconjugated MMAE AUC and Cmax at Cycle 6 were approximately 69% and 56% of the values at Cycle 1. The Ctrough values were low (<0.5 ng/mL) and there were no apparent changes after repeated Q3W dosing.

The AUC ratio MMAE/acMMAE in Cycles 1, 6, and 30 was 0.018, 0.0087, and 0.0071, respectively (=> 1.8%, 0.87% and 0.71%).

Dose Proportionality

In Cycle 1, there was a slightly less than dose proportional increase in Cmax and a dose proportional increase in AUC for all analytes (total antibody, acMMAE and MMAE) over a dose range of 0.1 to 2.4 mg/kg.

Based on the results of the pop PK analysis, the acMMAE PK is expected to be linear at doses ≥ 1.8 mg/kg after multiple dosing.

Distribution

The typical acMMAE central volume (V1) was 3.15 litres.

The mean plasma protein binding of MMAE in humans was 70.6% - 76.7%. It was independent of concentration between 1 and 100 nM. MMAE did not significantly distribute into human red blood cells (whole blood/plasma ratio: 1.34 – 1.65).

Metabolism

In vitro Data

MMAE was metabolised by CYP3A4/5. Fifteen MMAE metabolites were identified in human liver microsomes (HLM). The main (inactive) metabolites appeared to be M3, M13, M14, M15, and M17, formed by O-demethylation, N-demethylation, oxidation, or oxidation and dehydrogenation or dehydrogenation.

Clinical Data

No clinical studies investigating MMAE metabolism and excretion were conducted.

Elimination

acMMAE:

The typical value of the non-specific linear clearance (CLNS) was 0.9 litres/day at the end of Cycle 6.

Based on simulations with the final pop PK model, CLNS was the major clearance pathway of acMMAE after 1.8 mg/kg Q3W dosing. After Cycle 1, 82.7% of the dose was eliminated by CLNS. For the total cumulative dose administered for 6 cycles, 95.2% of the dose was eliminated by CLNS.

The contribution of the other two elimination pathways was lower: After Cycle 1 dosing, 15.2% of the dose was eliminated by linear exponentially-declining clearance (CLt) and 2% of the dose by the Michaelis Menten pathway. For the total cumulative dose administered for 6 cycles, 2.9% of the dose was eliminated by CLt and 1.9% of the dose was eliminated by the Michaels Menten pathway.

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From a mechanistic point of view, the time-dependent and Michaelis Menten components of the clearance were associated with changes in the disease state and target-mediated disposition. As expected, the non-linear processes were more pronounced during the first treatment cycle. But even then, their contribution was low compared to the non-specific linear acMMAE clearance. This means that the acMMAE PK is largely linear at doses ≥ 1.8 mg/kg.

The mean acMMAE half-life after 1.8 mg/kg based on the values of the linear clearance at Cycle 6 was 12.7 days.

MMAE:

Due to its toxicity, the direct administration of MMAE was not possible. Therefore, only apparent parameters were estimated, as the acMMAE-MMAE conversion fraction was unknown. The apparent linear clearance estimate of MMAE was 1.89 L/h, i.e. it was considerably faster than acMMAE clearance. The unconjugated MMAE PK was mainly driven by the dissociation/cleavage from polatuzumab.

The acMMAE-MMAE conversion fraction was 13.9% higher at the beginning of treatment compared to repeated dosing.

Special Populations

The final PopPK model included the following covariates potentially affecting acMMAE PK: prior treatment, tumour sum of product of perpendicular diameters, weight, B-cell count, gender, serum albumin, therapy (=> monotherapy versus combination therapy) and race. The final PopPK model included the following covariates potentially affecting the “formation” of MMAE: weight, gender, prior treatment, therapy, hepatic function, serum albumin and ECOG score.

As expected for an antibody, body weight had the largest impact on Cycle 6 acMMAE AUC and Cmax. Combined treatment with rituximab or obinutuzumab had the largest impact on acMMAE Ctrough.

Body weight also had the largest effect on Cycle 6 MMAE AUC, Cmax or Ctrough. Consequently, POLA is dosed by body weight.

The results of the simulations regarding the impact of covariates on the acMMAE or MMAE exposure are summarised below:

acMMAE

Comparison (Geometric Mean Ratio (90% CI)), Source	**AUC**	**Cmax**	**Ctrough**
BWT ≥ 100 kg/ BWT < 100 kg	1.08 (1.03-1.14)	1.17 (1.14-1.21)	1.17 (1.14-1.21)
Males/ Females	0.956 (0.926-0.988)	0.923 (0.902-0.944)	0.923 (0.902-0.944)
Age ≥ 65 / Age < 65	0.974 (0.944-1)	0.947 (0.926-0.97)	0.996 (0.924-1.07)
FL/ DLBCL	1.04 (1.01-1.07)	1.03 (1.01-1.05)	1.01 (0.94-1.09)
Asian/ Non-Asian	0.988 (0.94-1.04)	0.998 (0.944-1.05)	1.07 (0.971-1.19)
Asia/ Non-Asia	0.961 (0.897-1.03)	0.939 (0.87-1.01)	1.10 (0.952-1.27)
With Bendamustine/ Without Bendamustine,	1.05 (1.02-1.08)	0.987 (0.964-1.01)	1.19 (1.11-1.27)
Mild Hepatic Impairment/ Normal	0.96 (0.906-1.02)	0.962 (0.924-1)	0.927 (0.797-1.08)
Moderate Hepatic Impairment/ Normal	0.969 (0.802-1.17)	0.98 (0.925-1.04)	0.916 (0.613-1.37)
Mild Renal Impairment/ Normal	0.991 (0.956-1.03)	0.964 (0.939-0.99)	1.06 (0.974-1.15)

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Comparison (Geometric Mean Ratio (90% CI)), Source	AUC	Cmax	Ctrough
Moderate Renal Impairment/ Normal	0.985 (0.944-1.03)	0.909 (0.884-0.935)	1.09 (0.98-1.21)
Rituximab or Obinutuzumab Combination/ Monotherapy	1.25 (1.16-1.34)	1.06 (1.02-1.1)	**1.75 (1.45-2.11)**
Rituximab Combination/ Monotherapy	1.24 (1.15-1.33)	1.05 (1.01-1.09)	**1.73 (1.43-2.1)**
Obinutuzumab Combination/ Rituximab	1.02 (0.988-1.05)	1.03 (1.01-1.06)	1.02 (0.958-1.09)
Treatment-Naïve/ Relapsed or Refractory	0.924 (0.894-0.955)	0.846 (0.817-0.876)	0.902 (0.84-0.969)
ADA Positive/ ADA Negative	0.928 (0.798-1.08)	1.07 (1-1.15)	0.809 (0.576-1.14)

None of the covariates investigated had a major impact on the acMMAE exposure. Therefore, from a pharmacokinetic point of view, no dose adjustments for these covariates were required.

However, it should be borne in mind that the PopPK dataset included only 5 patients with moderate hepatic impairment. This was appropriately reflected in the information for healthcare professionals. The same applied for mild and moderate renal impairment.

MMAE

Comparison (Geometric Mean Ratio (90% CI)), Source	AUC	Cmax	Ctrough
BWT ≥ 100 kg/ BWT < 100 kg	1.27 (1.15-1.39)	1.27 (1.16-1.39)	1.15 (1.01-1.32)
Males/ Females	1.04 (0.966-1.12)	1.04 (0.966-1.12)	1.04 (0.966-1.12)
Age ≥ 65 / Age < 65	1.08 (1-1.17)	1.05 (0.976-1.12)	1.16 (1.06-1.28)
FL/ DLBCL	0.83 (0.771-0.893)	0.863 (0.808-0.922)	0.795 (0.725-0.871)
Asian/ Non-Asian	0.814 (0.688-0.963)	0.831 (0.708-0.975)	0.798 (0.663-0.96)
Asia/ Non-Asia	0.75 (0.647-0.87)	0.768 (0.669-0.881)	0.745 (0.641-0.865)
With Bendamustine/ Without Bendamustine,	0.862 (0.799-0.929)	0.864 (0.808-0.923)	0.883 (0.803-0.971)
Mild Hepatic Impairment/ Normal	**1.40 (1.22-1.6)**	**1.34 (1.2-1.51)**	**1.50 (1.22-1.83)**
Moderate Hepatic Impairment/ Normal	1.17 (0.655-2.1)	1.16 (0.673-2.01)	1.11 (0.596-2.05)
Mild Renal Impairment/ Normal	1.08 (0.989-1.18)	1.03 (0.952-1.12)	1.19 (1.07-1.33)
Moderate Renal Impairment/ Normal	1.06 (0.966-1.17)	1.01 (0.926-1.1)	1.01 (0.926-1.1)
Rituximab or Obinutuzumab Combination/ Monotherapy	**0.639 (0.564-0.723)**	**0.609 (0.538-0.69)**	**0.719 (0.612-0.844)**
Rituximab Combination/ Monotherapy	**0.627 (0.551-0.713)**	**0.597 (0.525-0.679)**	**0.706 (0.597-0.835)**
Obinutuzumab Combination/ Rituximab	1.05 (0.967-1.13)	1.05 (0.981-1.12)	1.04 (0.943-1.16)
Treatment-Naïve/ Relapsed or Refractory	**0.742 (0.679-0.812)**	**0.735 (0.679-0.796)**	**0.721 (0.645-0.807)**
ADA Positive/ ADA Negative	1.1 (0.863-1.4)	1.24 (0.918-1.68)	0.887 (0.674-1.17)

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None of the covariates investigated had a major impact on the MMAE exposure. Slight increases were observed in patients with mild hepatic impairment. The MMAE exposure was decreased in the presence of rituximab or obinutuzumab. It was also slightly lower in treatment-naïve patients compared to relapsed or refractory patients.

Interactions

A total concentration of 7 ng/mL MMAE corresponds to 10 nM. Mean simulated MMAE concentrations after 1.8 mg/kg Q3W were 4.08 ng/mL (5.8 nM) in Cycle 1 and 2.27 ng/mL in Cycle 6. Assuming a free fraction of 30%, unbound Cmax in Cycle 1 after 1.8 mg/kg was 1.74 nM. Cmax,u * 50 = 87 nM (0.087 µM).

In vitro Data – Inhibition of hepatic CYPs by MMAE

MMAE showed direct and time-dependent inhibition of CYP3A4 (IC_{50} of 10 µM and 0.4 µM, respectively). None of the other CYPs investigated (1A2, 2B6, 2C8, 2C9, 2C19 and 2D6) was inhibited by MMAE at concentrations up to 100 µM.

In vitro Data – Induction of hepatic CYPs by MMAE

At concentrations up to 1 µM, MMAE did not induce CYP1A2, 2B6 or 3A4. However, there was a concentration-dependent decrease in both mRNA and CYP activity, which was not caused by MMAE related cell toxicity.

Physiology-based PK Modelling

A physiology-based PK (PBPK) model was developed and qualified using the data for pinatuzumab vedotin, brentuximab vedotin, and polatuzumab vedotin. The antibodies of these three ADCs bind to different targets (pinatuzumab to CD22, brentuximab to CD30, polatuzumab to CD79b), but all three ADCs contain MMAE connected to the antibody with the same linker.

A clinical interaction study investigating the impact of ketoconazole or rifampicin on MMAE exposure is available for brentuximab vedotin. The PBPK model predicted the results of the study reasonably well. It was used to simulate these interactions for polatuzumab vedotin. The simulations indicated 1.18-fold and 1.48-fold increases in MMAE Cmax and AUC, respectively, in the presence of ketoconazole. In the presence of rifampicin, the simulation indicated 29% and 49% decreases in MMAE Cmax and AUC, respectively. An increase in MMAE exposure in plasma is likely to be associated with a higher incidence of adverse events (AEs). Therefore, patients receiving concomitant strong CYP3A4 inhibitors should be closely monitored for toxicity.

As MMAE is supposed to be delivered into B cells for action, and the impact of decreased MMAE plasma concentrations on efficacy is unknown.

In vitro Data – MMAE as Substrate or Inhibitor of Drug Transporters

Transporter	Substrate	Inhibitor
Pgp	**Yes**	Unlikely at therapeutic exposure
BCRP	No	No (up to 5 µM)
OATP1B1	No	No (up to 5 µM)
OATP1B3	No	No (up to 5 µM,)
OCT2	No	Maximum inhibition at 5 µM: 23%
OCT1	Not investigated	Maximum inhibition at 5 µM: 29%
OAT1	No	No (up to 5 µM,)
OAT3	No	No (up to 5 µM)

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Transporter	Substrate	Inhibitor
BSEP	Not investigated	No (up to 5 µM)
MRP2	No	No (up to 5 µM)

Clinical Data – Impact of other Drugs on acMMAE or MMAE

The respective results of the PopPK analyses were summarised above. The co-administration of bendamustine, rituximab, or obinutuzumab had no major impact on acMMAE exposure.

The co-administration of bendamustine also had no major impact on the MMAE exposure but, in the presence of rituximab or obinutuzumab, the MMAE exposure was reduced by up to 40%.

Clinical Data – Impact of acMMAE/MMAE on other Drugs

Supportive data from NCAs:

Impact of POLA on bendamustine Cycle 1 Cmax and AUC: POLA did not appear to affect bendamustine PK.

Impact of POLA on rituximab Cycle 1 Cmax and AUC, Cycle 2, and 4 Ctrough: POLA did not appear to affect rituximab PK.

Impact of POLA on cyclophosphamide and doxorubicin Cmax and Ctrough in Cycle 3: POLA did not appear to have a major impact on the exposure of cyclophosphamide or doxorubicin.

Pharmacodynamics

No dedicated tQT study was conducted for POLA. Instead, descriptive and pharmacometric analyses of selected electrocardiographic data were provided. The analysis included 996 QTcF measurements from 209 patients. The descriptive statistical evaluation of ΔQTcF showed a maximum mean prolongation of 10.31 ms with a 90% CI of 6.9 to 13.72 ms at Cycle 3 Day 2 post-dose. In contrast to a classical tQT study, the dataset did not include a placebo or active control arm. Considering this and the higher variability of the data in patient studies, the generally accepted threshold of concern is 20 ms (instead of 10 ms for a tQT study) for oncology compounds.

The Entity-Relationship (ER) analysis showed a statistically significant, positive slope for acMMAE and total antibody, but not for MMAE concentrations. The models described the data and their variability reasonably well.

Co-administered rituximab or obinutuzumab, treatment cycle and study were investigated as covariates of intercept and slope. Only the treatment cycle reached statistical significance.

The results of the ER analysis were in good agreement with the descriptive statistical evaluation of the data.

POLA had only a small impact on heart rate at doses up to 2.4 mg/kg.

In summary, POLA did not appear to have a major impact on QTcF at therapeutic exposure.

6.3 Dose Finding and Dose Recommendation

The application for marketing authorisation of PV for relapsed or refractory DLBCL was submitted in a comparably early phase of the clinical development programme of polatuzumab vedotin. Dose finding in various B-cell malignancies and in various drug combination partners was ongoing.

The pertinent phase 1a trial for this application was study DCS4968g initiated in 2011. A dose escalation/expansion (PV mono, PV in combination with rituximab) was conducted in B-cell NHL and CLL over a dose range of 0.1 to 2.4 mg/kg, with the starting dose based on cynomolgus monkey data, and an unlimited duration of therapy was allowed in case of tolerability. Two DLTs of neutropenia or infections were seen at 2.4 mg/kg, and peripheral neuropathy (PNP) was seen to be associated with dose and duration of exposure. According to the applicant, in September 2014 a clinical trial hold at the dose of 2.4 mg/kg was issued by the FDA. The following trials and cohorts focused on a dose of 1.8 mg/kg and a maximum of 6 cycles of therapy. The current application for relapsed/refractory (r/r) DLBCL in combination with bendamustine and rituximab is based on two cohorts of an adaptive

phase 1b/2 trial GO29365 in which a dose of 1.8 mg/kg was chosen in all regimens/cohorts opened so far. With the data at hand it could not conclusively be assessed whether 1.8 mg/kg d1 given every 21 days in DLBCL (or every 28 days in follicular lymphoma) is the most appropriate or rationalised dosing scheme in combination with bendamustine 90mg/m2 d1 and 2 and rituximab 375mg/m^2 d1 or in combination with other partners.

6.4 Efficacy

The pivotal trial comprised a multi-cohort phase 1b/phase 2 trial, GO29365. Supporting data for this marketing authorisation application are derived from 4 arms of this trial. Enrolled patients had received a median number of two prior lines (range 1 to 7) and had transplant-ineligible relapsed or refractory DLBCL.

Following a phase 1b safety run-in, PV in combination with Bendamustine and Rituximab (PV-BR) was investigated in the phase 2 part randomised 1:1 in N=40 (cohort C, BR-PV) and in N=40 patients treated with bendamustine and rituximab (cohort D, BR). Although BR is not approved in Switzerland for r/r DLBCL, it is considered an acceptable comparator arm and backbone for PV. PV was administered intravenously at a dose of 1.8 mg/kg on day 1 (d1), bendamustine 90mg/m^2 on d1 and d2 and rituximab 375mg/m^2 on d1, every 21 days for a maximum of 6 cycles.

During the randomised phase of trial GO29365, a liquid formulation of PV was used (cf. Clinical Pharmacology, Biopharmaceutical Development).

Subsequently, two additional non-randomised single arm cohorts G and H enrolled N=42 (cohort G) and N=64 (cohort H) patients with r/r DLBCL. In these cohorts, a lyophilised formulation of PV, which is identical to the commercialised formulation, was administered in combination with BR.

During assessment, Swissmedic requested additional analyses of the randomised cohorts (C and D) and the single-arm cohorts (G and H), investigating the commercial lyophilised formulation, in order to better understand the efficacy as well as the safety profile of the different formulations of PV in combination with BR.

The most recent analyses were derived from a data cutoff date of 07 July 2020, providing a median follow-up of 49.9 months for the randomised cohorts and 15.2 months for the non-randomised lyophilised formulation cohorts.

The primary endpoints were different between the various cohorts. The independent radiology review committee (IRC) assessed the complete response rate in PET-CT scans at the end of treatment (6-8 weeks after cycle 6, day 1, or last dose of study medication), the primary endpoint in the randomised cohorts, which was 42.5% (95%CI 27.0, 52.1) versus 17.5% (7.3, 32.8) for trial participants who received PV-BR (cohort C) and BR (cohort D), respectively. In the pooled single arm cohorts (G and H), complete response (CR) rate at the end of treatment was 38.7% (29.4, 48.6). Formal statistical hypotheses were not specified in the exploratory trial GO29365 and, consequently, statistical analyses conducted by the applicant were descriptive.

Median progression-free survival, median overall survival as well as overall survival rates at 12 months were, overall, numerically superior for patients receiving PV-BR over BR and, together with the CR rate at the end of treatment, considered as clinically meaningful in the disease context.
For more detailed trial characteristics and efficacy results please refer to the information for healthcare professionals (Fachinformation).

6.5 Safety

The safety profile appeared to be comparable between the liquid formulation of PV+BR, and the pooled cohorts using the commercial lyophilised formulation of PV+BR, with the main caveats of a substantially shorter follow-up and observation period in the latter arms and the overall small dataset. The most common side effects with Polivy in combination with bendamustine and rituximab, which may affect more than 3 in 10 people, were anaemia, thrombocytopenia, neutropenia, diarrhoea,

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nausea, tiredness, and peripheral neuropathy. Serious side effects (which may affect up to 1 in 10 people) include febrile neutropenia, fever, pneumonia, and sepsis.
Prophylactic administration of growth factor G-CSF (colony stimulating factor), antiviral drugs (coverage for herpes simplex virus and varicella zoster virus) and anti-pneumocystis drugs, from the beginning of treatment are recommended and should be maintained as long as clinically appropriate. PV must not be given to patients who have a severe infection. Rare, but potentially severe, side effects included progressive multifocal leukoencephalopathy (PML), tumour lysis syndrome, hepatotoxicity, and embryofoetal toxicity. For a full list of side effects of Polivy and warnings cf. the information for healthcare professionals.

In addition to routine reporting requirements, the applicant committed itself, at the request of Swissmedic, to submitting updated safety results separately for men and women in 2022 and 2023, and updated efficacy results in 2022.

6.6 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Beneficial Effects & Uncertainties - Clinical Pharmacology

The acMMAE and MMAE exposure increased proportionally to the administered dose over a dose range of 0.1 – 2.4 mg/kg. acMMA showed minimal accumulation after 1.8 mg/kg Q3W. The MMAE concentrations decreased after multiple dosing. The POLA interaction potential is most likely low. From a purely pharmacokinetic point of view, no dose adjustments are required for the investigated covariates. POLA had no major effect on QTcF or heart rate at therapeutic exposure.

No PK data were available on patients with severe hepatic or renal impairment. The PopPK dataset included only 5 patients with moderate hepatic impairment. There were too few ADA-positive patients to draw conclusions regarding the impact on acMMAE exposure.

No human MMAE mass balance and metabolism data were available. No clinical interaction data were available.

Beneficial Effects, Risks & Uncertainties - Clinical Assessment

With the cumulative data at hand from the exploratory phase 1b / phase 2 trial GO29365, including 40 patients treated with the investigational liquid formulation of PV in combination with BR, and 106 patients treated with the commercial lyophilised formulation of PV, efficacy appears to be superior to BR as well as historic controls (SCHOLAR study) and, overall, comparable with approved CAR-T cell products, considering the ITT population of pivotal CAR-T trials. PV+Bendamustine+Rituximab is an additional option for patients with relapsed or refractory DLBCL after ≥ 1 prior line of therapy who are not candidates for autologous stem cell transplantation.

The safety profile of lyophilised PV+BR seems to be acceptable in experienced hands. Haematotoxicity and infectious complications, together with peripheral neuropathy, are the most relevant adverse reactions to be monitored, based on the small safety database at hand. Patients with pre-existing neuropathy are at high risk of experiencing a worsening of their condition.

Uncertainty remains regarding (optimal) dose finding of PV in various diseases and with different combination partners. Limited patient numbers and no randomised data are available for the lyophilised formulation of PV. Long-term efficacy and safety are unknown. Safety in routine settings, including possible occurrence of rare side effects, cannot be conclusively estimated based on the small safety dataset at hand. A clinically relevant higher toxicity for female patients compared to male patients cannot be excluded at present.

Conclusions - Clinical Pharmacology

The available data did not raise any specific concerns. The pharmacokinetics of acMMAE reflected the PK of an antibody binding to a cellular target, exhibiting target-mediated disposition. The MMAE

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plasma concentrations were very low compared to the acMMAE concentrations, indicating that MMAE was mostly delivered to the target cells.

Bioequivalence regarding the exposures to acMMAE and unconjugated MMAE was demonstrated between the liquid and the lyophilised PV formulation.

Conclusions - Clinical Assessment

The benefit-risk assessment is positive for patients with DLBCL after ≥ 1 prior line of therapy and ineligibility for autologous haematopoietic stem cell transplantation.

6.7 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to polatuzumab vedotin was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the *"Undesirable effects"* section for advice on the reporting of adverse reactions.

Polivy®

Composition

Active substances

Polatuzumab vedotin (produced using genetically engineered CHO [Chinese Hamster Ovary] cells).

Excipients

Accidum succinicum, natrii hydroxidum, saccharum, polysorbatum 20 (produced from genetically modified maize).

1 ml of reconstituted solution contains 0.31 mg sodium, i.e. 0.47 mg sodium per 30 mg vial or 2.18 mg sodium per 140 mg vial.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.

Polivy is a white to grayish-white lyophilized cake supplied in single-dose vials. 1 vial contains 30 mg (38 mg for the overfill volume) or 140 mg (150 mg for the overfill volume) polatuzumab vedotin. After reconstitution, the Polivy concentrate contains 20 mg/mL polatuzumab vedotin.

Indications/Uses

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

Dosage/Administration

General

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 technique 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 section *"Instructions for handling"*). 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.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

The recommended dose of Polivy is 1.8 mg/kg given as an intravenous infusion every 3 weeks 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 of each cycle and the recommended dose of rituximab is 375 mg/m^2 on Day 1 of each cycle when bendamustine is used with Polivy.

If not already premedicated, administer premedication with an antihistamine and anti-pyretic 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.

Dose modification due to adverse reactions/interactions

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. 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.

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. If ANC recovers to >1000/μL on or before Day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1000/μL 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	Hold all treatment until platelets recover to >75,000/μL. If platelets recover to >75,000/μL on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to >75,000/μL 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

[a]If primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.

Special dosage instructions

Patients with impaired hepatic function

No dose adjustment is required when Polivy is administered to patients with mildly impaired hepatic function (total bilirubin higher than the ULN and lower or equivalent to 1.5 times ULN or aspartate aminotransferase [AST] higher than the ULN) (see section "*Kinetics in specific patient groups*").

The safety and efficacy of Polivy has not been formally investigated in patients with moderately or severely impaired hepatic function [AST >2.5 times ULN, ALT >2.5 times ULN or total bilirubin >1.5 times ULN]. However, MMAE exposure is likely to be elevated in these patients. The use of Polivy is to be avoided in patients with moderately or severely impaired hepatic function [total bilirubin higher than 1.5 times ULN] *(*see section "*Kinetics in specific patient groups*"*).*

Patients with impaired renal function

No dose adjustment of Polivy is required in patients with mildly to moderately impaired renal function (creatinine clearance (CrCL) ≥30mL/min). There are no dose recommendations for patients with severely impaired renal function (CrCL <30mL/min) due to limited data *(*see section "*Kinetics in specific patient groups*"*).*

Elderly patients

No dose adjustment of Polivy is required in patients ≥ 65 years of age *(*see section "*Kinetics in specific patient groups*"*).*

No differences were determined overall between patients aged ≥ 65 and younger patients in relation to safety and efficacy.

Children and adolescents

The safety and efficacy of Polivy in children and adolescents (<18 years) has not been established.

Delayed 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 3-week interval between doses.

Contraindications

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

Warnings and precautions

Myelosuppression

Severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy as early on as during the first cycle of treatment (see section *"Undesirable effects"*). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with Polivy (see section *"Undesirable effects"*). Differential 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 *"Dosage/Administration")*.

Peripheral Neuropathy

Peripheral neuropathy has already been reported in patients treated with Polivy during the first cycle of treatment, and the risk increases with sequential doses (see section *"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 *"Dosage/Administration"*).

Infections

Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including *pneumocystis jirovecii* and other mycotic pneumonias), bacteremia, sepsis, herpes simplex infection, and cytomegalovirus infection have been reported in patients treated with Polivy (see section *"Undesirable effects")*. Patients should be closely monitored during treatment for signs of bacterial, mycotic, 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 in association with Polivy treatment (see section *"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 interrupted 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-Fetal 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 *"Pregnancy", "Mechanism of Action"* and *"Reproductive Toxicity"*). Advise a pregnant woman of the risk to the fetus.

Females of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose. 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 *"Impairment of Fertility", "Genotoxicity and Reproductive Toxicity"*).

Hepatic Toxicity

Severe cases of hepatic toxicity have occurred in patients treated with Polivy, including elevations of transaminases and/or bilirubin, that are consistent with hepatocellular injury (ALT or AST >3 time higher than the ULN and bilirubin >2 times higher than the ULN).

Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Liver enzymes and bilirubin level should be monitored (see section *"Special dosage instructions"* and *"Patients with impaired hepatic function"*).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially “sodium-free“.

Interactions

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

In-vitro studies

In-vitro studies have demonstrated that MMAE is a CYP 3A4/5 substrate, but does not induce any important CYP enzymes. MMAE is a weak, time-dependent CYP3A4/5 inhibitor, but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations.

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

MMAE is an *in-vitro* P-gp substrate, but not an *in-vitro* substrate for OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MRP2 and BCRP.

MMAE does not inhibit P-gp, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, MRP2 or BCRP *in-vitro* at clinically relevant concentrations.

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

Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE (monomethyl auristatin E) 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 administration of 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.

Pregnancy, lactation

Pregnancy

Polivy is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Polatuzumab vedotin can cause fetal harm based on the animal studies and the drug’s mechanism of action (see section *"Mechanism of Action"*).

Animal data

In animal studies, MMAE caused genotoxicity and embryo-fetal toxicity (see section *"Genotoxicity"* and *"Reproductive Toxicity"*).

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 polatuzumab vedotin on milk production or its presence in breast milk. Since many active substances are excreted in human milk and because of the potential for Polivy to cause serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding during treatment with Polivy and not breastfeed for at least 3 months after the final dose.

Fertility

Based on animal studies, polatuzumab vedotin may impair male reproductive function and fertility (see section *"Impairment of fertility"*).

Polatuzumab vedotin caused testicular toxicity in preclinical studies and may impair male reproductive function and fertility. Men who are receiving treatment with Polivy are therefore advised to preserve sperm samples by freezing them before starting treatment.

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 (see section *"Genotoxicity"* and *"Reproductive Toxicity"*).

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 (see section *"Genotoxicity"* and *"Reproductive Toxicity"*).

Effects on ability to drive and use machines

Polivy has 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 *"Warnings and Precautions"* and *"Undesirable effects"*).

Undesirable effects

Summary of the safety profile

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), randomized patients (n = 39) and patients in the extension cohort (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 arms received a median of 5 cycles of treatment, whereas randomized patients in the comparator arm received a median of 3 cycles of treatment.

Tabulated summary of ADRs from clinical trials

ADRs are listed in Table 3 by MedDRA system organ class (SOC).

The most frequently reported adverse reactions (≥30%) in patients treated with Polivy in combination with BR were anemia, thrombocytopenia, neutropenia, diarrhea, nausea, and peripheral neuropathy. Serious adverse reactions were reported in 55.6% of patients treated with Polivy in combination with BR, of which the following occurred in ≥5% of patients: febrile neutropenia (9.3%), fever (7.9%), pneumonia (6.6%) and sepsis (6.6%).

The adverse reaction that led to treatment regimen discontinuation in >5% of patients was thrombocytopenia (6%).

Table 3: Summary of adverse reactions in previously treated patients with DLBCL under treatment with Polivy in combination with BR

Adverse reactions	**Frequency category**	**Polivy + bendamustine + rituximab n = 151**
System organ class		**All grades (%)**
Infections and infestations		
Pneumonia[a]	very common	14.6
Sepsis	very common	10.6
Upper respiratory tract infection	common	9.9
Herpes virus infection	common	5.3
Cytomegaly virus infection	common	2.1
Blood and lymphatic system disorders		
Neutropenia	very common	45.7
Thrombocytopenia	very common	32.5
Anemia	very common	31.8
Leukopenia	very common	15.2
Lymphopenia	very common	13.2
Febrile neutropenia	very common	11.3

Pancytopenia	common	3.3
Metabolism and nutrition disorders		
Decreased appetite	very common	25.8
Hypokalemia	very common	16.5
Hypoalbuminemia	common	6.0
Hypocalcemia	common	5.3
Hypophosphatemia	common	4.0
Nervous system disorders		
Peripheral neuropathy	very common	30.5
Dizziness	very common	11.3
Peripheral sensory neuropathy	common	7.3
Respiratory, thoracic and mediastinal disorders		
Cough	very common	15.9
Pneumonitis	common	1.3
Gastrointestinal disorders		
Diarrhea	very common	35.8
Nausea	very common	33.1
Constipation	very common	18.5
Abdominal pain	very common	17.9
Vomiting	very common	17.2
Upper abdominal pain	common	7.3
Elevated lipases	common	4.0
Hepatic and biliary disorders		

Elevated transaminases	common	7.3
Skin and subcutaneous tissue disorders		
Pruritis	common	9.3
Musculoskeletal and connective tissue disorders		
Arthralgia	common	4.0
General disorders and administration site conditions		
Fever	very common	28.5
Fatigue	very common	26.5
Asthenia	very common	11.9
Chills	common	4.6
Investigations		
Weight decreased	very common	13.9
Injury, poisoning and procedural conmplications		
Infusion-related reaction	very common	11.9

[a] Adverse reactions associated with fatal outcome.

Description of selected adverse reactions

Description of selected adverse drug reactions from clinical trials

Myelosuppression

While 4% of patients in the Polivy plus BR arms discontinued Polivy due to neutropenia, this was 2.6% of patients in the BR arm. 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 the BR arm.

Peripheral Neuropathy (PN)

In the Polivy plus BR arms, a Grade 1 PN event was reported in 15.9% of patients and a Grade 2 PN event in 12.6% of patients. In the BR arm, Grade 1 and 2 PN events were reported in 2.6% and 5.1% of patients, respectively. In the Polivy plus BR arms, 1 Grade 3 PN event was reported and no Grade 3 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 a 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 duration to the first occurrence of PN was 1.6 months, and 39.1% of patients with PN events reported event resolution over the further course (see section *"Warnings and Precautions"*).

Infections

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. 4 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 *"Warnings and Precautions"*).

Progressive Multifocal Leukoencephalopathy (PML)

One case of PML, which was fatal, occurred in a patient treated with Polivy plus bendamustine and obinutuzumab (combination not authorised in Switzerland). This patient had three prior lines of therapy that included anti-CD20 antibodies (see section *"Warnings and Precautions"*).

Hepatic toxicity

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

Gastrointestinal Toxicity

Gastrointestinal toxicity was 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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no experience with overdose in human clinical trials. The highest dose tested to date is 2.4 mg/kg administered as an intravenous infusion. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Properties/Effects

ATC code

L01XC37

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. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 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 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

The efficacy of Polivy plus BR was evaluated in an international, multicenter, open-label phase 1b/2 study (GO29365) which included two randomized cohorts (each n = 40) and two extension cohorts (n = 42 and n = 64) of patients with pretreated DLBCL.

Patients in the randomized cohort who were treated with Polivy in combination with bendamustine and rituximab received a liquid formulation of Polivy. Treatment in the extension cohorts was carried out with the commercially available lyophilized formulation of Polivy.

Eligible patients were not candidates for autologous hematopoietic stem cell transplant (HSCT). The most common reasons for this were age (42%), an inadequate response to salvage therapy (27%) and therapeutic failure after an earlier HSCT (16%). The patients had relapsed or refractory disease after receiving at least one prior systemic chemotherapy regimen. One patient had previously received CART-cell therapy. 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 remission (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.

Randomised and extension cohorts

In the 1:1 randomised cohorts (n = 80), the median age was 69 years (range: 30 to 86 years) and 66% of patients were male. In the extension cohorts (n = 106), the median age was 70 years (range: 24 to 94 years) and 49% were male. The majority of patients in both cohorts had DLBCL not otherwise specified (98% in the randomized cohort and 91% in the extension cohorts), including activated B-cell-like DLBCL (48%) and germinal centre B-cell-like DLBCL (40%). The median number of prior therapies was 2 (range: 1 - 7) in the entire cohort. The proportion of patients with refractory disease in comparison to the previous line of therapy was 70.5%. 41.1% of patients had received three or more prior therapies.

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

	Bendamustine + rituximab N = 40	**Polivy + bendamustine + rituximab N = 40**	**Polivy + bendamustine + rituximab N = 106**
	Randomized Cohorts		**Extension Cohorts**
Median observation time	**42 months**		**9.7 months**
Primary Endpoint			
*(IRC-assessed) at end of treatment**			
Patients with CR (%)	7 (17.5)	16 (40.0)	42 (39.6)
p-value‡ (descriptive***)	0.0261		-
Further Endpoints			
Overall Survival			
Number (%) of patients with event	29 (72.5)	26 (65.0)	51 (48.1)
Median OS (95% CI), months	4.7 (3.7, 8.3)	12.4 (9.0, 32)	11.0 (8.3, 14.2)
HR [95% CI]	0.42 [0.24, 0.73]		-
12-month OS rate (%)	23.8	51.9	-
95% CI	(8.8, 38.8)	(35.8, 67.9)	
Progression-free survival (PFS) (IRC-assessed)			
Number (%) of patients with event	32 (80.0)	30 (75.0)	64 (60.4)
Median PFS (95% CI), months	3.7 (2.1, 4.5)	9.2 (6.1, 13.9)	6.1 (5.1, 8.0)
HR [95% CI]	0.38 [0.22, 0.65]		-
12-month PFS rate (%)	15.1	42.1	-
95% CI	(3.0, 27.3)	(26.4, 57.8)	
Duration of response (DOR) (IRC-assessed)			

Number of responders included in analysis	10 (25)	25 (62.5)	60 (56.6)
(CR/PR)	8 (80.0)	17 (68.0)	22 (36.7)
Number (%) of responders with event			
Median DOR (95% CI), months	10.2 (4.0, 19.6)	10.9 (5.7, 40.7)	6.2 (5.4, 11.6)
HR [95% CI]	0.60 [0.25, 1.43]		-

IRC: Independent Review Committee; CI: Confidence Interval, HR: Hazard Ratio; CMH Cochran-Mantel-Haenszel; OS: Overall survival; PFS: Progression-Free Survival; DOR: Duration of Response, CR: Complete Response, PR: Partial Response.

* Based on 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.

*** CMH chi-square test, stratification by duration of response to prior therapy (≤12 months vs >12 months).

‡ Descriptive p-value.

Additional information

Cardiac electrophysiology

Polatuzumab vedotin did not cause any clinically relevant prolongation to the mean QTc interval based on the ECG data from two unblinded studies conducted in patients with previously treated B-cell lymphoma.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. A total of 8 out of 134 (6.0%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points in all arms of study GO29365 (excluding the extension cohort). 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.

Pharmacokinetics

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 [63]. 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.

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. 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.

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 liters, 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-plasma ratio is 0.79 to 0.98.

Metabolism

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

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. The terminal half-life at cycle 6 was approximately 12 days (95% CI: 8.1-19.5 days) for acMMAE. The terminal half-life for MMAE in cycle 1 was approximately 4 days.

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

Kinetics in specific patient groups

Hepatic impairment

In patients with mild hepatic impairment [AST or ALT >1.0 to 2.5×ULN or total bilirubin >1.0 to 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 *"Dosage/Administration")*.

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 *"Dosage/Administration"*).

Elderly Patients

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 and adolescents

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

Preclinical data

Carcinogenicity

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

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.

Reproductive toxicity

No dedicated teratogenicity studies in animals have been performed with Polivy. However, MMAE was evaluated in rats in a GLP embryo-fetal developmental and toxicokinetic study, in which pregnant rats received 2 intravenous doses of 0.2 mg/kg MMAE during the period of organogenesis on gestational day 6 and 13. Treatment with MMAE at 0.2 mg/kg caused fetal external 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 three weeks.

Impairment of 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 were not reversible 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.

Other information

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 contact surfaces made of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP) or polytetrafluoroethylene (PTFE) or with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

Shelf life

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

Shelf life after opening

See section *"Instructions for handling".*

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

Special precautions for storage

Vials

Store in the refrigerator (2-8 °C).

Store in the original packaging.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

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 concentrate 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 ready diluted Polivy.

Reconstitution

1. Using a sterile syringe, slowly inject 1.8 mL sterile water for injection into the 30 mg Polivy vial or 7.2 mL of sterile water for injection into the 140 mg Polivy vial to yield a single-dose concentrate 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 the contents are completely dissolved. *Do not shake*.

3. Inspect the reconstituted concentrate for discoloration and particulate matter. It should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted concentrate is discolored, cloudy, or contains visible particulates.

From a microbiological point of view, the reconstituted concentrate should be used immediately. If it is 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 concentrate 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. The polatuzumab vedotin concentrate 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 concentrate (20 mg/mL) needed based on the required dose:

$$\text{Volume} = \frac{\text{Polivy dose (1.8 or 1.4 mg/kg) X patient's weight (kg)}}{\text{Concentration of concentrate in the vial (20 mg/mL)}}$$

3. Withdraw the required volume of concentrate 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 ready diluted 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 ready diluted 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.

Disposal of unused/expired medicines

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).

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

Authorisation number

67165 (Swissmedic).

Packs

1 injection vial containing 30 mg polatuzumab vedotin [A]

1 injection vial containing 140 mg polatuzumab vedotin [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

Date of revision of the text

June 2021.