Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and is to be used in combination with other medicines prescribed off-label. The information is provided to assist the doctor in prescribing unlicensed medicines. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Polatuzumab vedotin 140 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 140 mg of polatuzumab vedotin.

After reconstitution (see section 6.6), each mL contains 20 mg of polatuzumab vedotin.

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

Excipient with known effect
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. 'essentially sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Preservative-free, white to greyish-white lyophilized cake.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indications

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

4.2 Posology and method of administration

Polatuzumab vedotin must be initiated and supervised by specialist physicians experienced in the treatment of cancer patients.

Posology

The recommended dose of polatuzumab vedotin is 1.8 mg/kg, administered by intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles.

Polatuzumab vedotin should be administered on Day 2 of Cycle 1 and on Day 1 of Cycles 2-6. Bendamustine should be administered intravenously at the dose of 90 mg/m^2/day on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2-6. Rituximab should be administered intravenously at the dose of 375 mg/m^2 on Day 1 of Cycles 1-6.

Premedication with an antihistamine and anti-pyretic should be administered to patients prior to polatuzumab vedotin. The initial dose of polatuzumab vedotin 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

polatuzumab vedotin 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.

Please also refer to the full prescribing information of the combination products.

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

Dose modifications
The infusion rate of polatuzumab vedotin should be slowed or interrupted if the patient develops an infusion-related reaction. Polatuzumab vedotin should be discontinued immediately and permanently if the patient experiences a life-threatening reaction.

For dose modifications for peripheral neuropathy (section 4.4) see Table 1.

Table 1: Polatuzumab vedotin dose modifications for peripheral neuropathy (PN)

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

For dose modifications for myelosuppression see Table 2.

Table 2: Polatuzumab vedotin, bendamustine and rituximab dose modifications for myelosuppression

Severity of myelosupression on Day 1 of any cycle	**Dose modification[1]**
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 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

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

Special populations

Elderly
No dose adjustment of polatuzumab vedotin is required in patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment of polatuzumab vedotin is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30mL/min due to limited data.

Hepatic impairment
The administration of polatuzumab vedotin in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN) should be avoided.
No adjustment in the starting dose is required when administering polatuzumab vedotin to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or AST greater than ULN).

Paediatric population
The pharmacokinetics, safety and efficacy in children and adolescents less than 18 years have not been established. No data are available.

Method of administration

Polatuzumab vedotin must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. It should be administered as an intravenous infusion through a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 micrometer pore size) and catheter. Polatuzumab vedotin must not be administered as intravenous push or bolus.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the EAMS and batch numbers of the administered product should be clearly recorded in the patient file.

Myelosupression
Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with polatuzumab vedotin as early as the first cycle of treatment. Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anaemia can also occur Complete blood counts should be monitored prior to each dose of polatuzumab vedotin and combined medicines. More frequent lab monitoring and/or treatment delays or discontinuation should be considered for patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see section 4.2).

Peripheral neuropathy (PN)
Peripheral neuropathy has been reported in patients treated with polatuzumab vedotin as early as the first cycle of treatment, and the risk increases over the cycles. Patients with pre-existing peripheral neuropathy may experience worsening of this condition. Peripheral neuropathy reported with treatment with polatuzumab vedotin 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, paraesthesia, 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 polatuzumab vedotin (see section 4.2).

Infections
Serious, life threatening or fatal infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia), bacteraemia, sepsis, herpes infection, and

cytomegalovirus infection have been reported in patients treated with polatuzumab vedotin and/or bendamustine (see section 4.8).

Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections. Anti-infective prophylaxis should be considered. Polatuzumab vedotin and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

Progressive multifocal leukoencephalopathy (PML)
PML has been reported with polatuzumab vedotin treatment (see section 4.8) and/or anti-CD20 agents. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. Polatuzumab vedotin and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumour lysis syndrome (TLS)
Patients with high tumour burden and rapidly proliferative tumour may be at increased risk of tumour lysis syndrome. Appropriate measures in accordance with local guidelines should be taken prior to treatment and patients should be monitored closely for tumour lysis syndrome during treatment with polatuzumab vedotin.

Hepatic toxicity
Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with polatuzumab vedotin (see section 4.8). Preexisting liver disease, elevated baseline liver enzymes, and concomitant medicinal products may increase the risk. Liver enzymes and bilirubin level should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug interactions with co-medications that are CYP3A4 inhibitors, substrates or inducers and co-medications that are P-gp inhibitors
Based on physiological-based pharmacokinetic model simulations of MMAE released from polatuzumab vedotin, strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Caution is advised in case of concomitant treatment with CYP3A4 inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities. Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g., midazolam). Strong CYP3A inducers (e.g., rifampicin) may moderately decrease the AUC of unconjugated MMAE.

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 polatuzumab vedotin. Concomitant rituximab is associated with increased antibody conjugated MMAE (acMMAE) plasma AUC by 24% and decreased unconjugated MMAE plasma AUC by 37%, based on population PK analysis. No dose adjustment is required. Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

4.6 Fertility, pregnancy and lactation

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

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

Pregnancy
There are no data in pregnant women using polatuzumab vedotin. Polatuzumab vedotin 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 animal studies and its mechanism of action (see sections 5.1 and 5.3).

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

Fertility
Based on animal studies, polatuzumab vedotin may impair male reproductive function and fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Polatuzumab vedotin may have a minor influence on the ability to drive and use machines. Infusion related reactions, peripheral neuropathy, fatigue, and dizziness may occur during treatment with polatuzumab vedotin (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile
A total of 588 patients have received polatuzumab vedotin in clinical trials. The adverse drug reactions (ADRs) described in this section were identified in relapsed/refractory DLBCL patients (n=45) from the pivotal clinical trial GO29365 in combination with rituximab and bendamustine (BR).

The most frequently reported (≥ 30%) ADRs were anaemia, thrombocytopenia, neutropenia, fatigue, diarrhoea, nausea, pyrexia and peripheral neuropathy. ADRs leading to treatment regimen discontinuation in > 5% of patients were thrombocytopenia (9%) and neutropenia (7%).

Tabulated summary of adverse drug reactions from clinical trials
The Adverse Drug Reactions (ADRs) are listed below by MedDRA system organ class (SOC) and categories of frequency. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10).

Table 3: Summary of adverse drug reactions occurring in the pivotal trial in DLBCL patients treated with polatuzumab vedotin in combination with BR

Infections and Infestations (SOC)	
Very common	pneumonia[a] (including pneumocystis jirovecii, cytomegaloviral, pneumococcal pneumonia)
Common	upper respiratory tract infection (including nasopharyngitis, rhinovirus infection, sinusitis), herpes virus infection (including herpes zoster, herpetic meningoencephalitis)
Blood and Lymphatic System Disorders (SOC)	
Very common	anaemia, neutropenia, thrombocytopenia, febrile neutropenia, leukopenia, lymphopenia
Common	pancytopenia
Metabolism and Nutrition Disorders (SOC)	
Very common	decreased appetite, hypokalaemia, hypoalbuminemia, hypocalcaemia

Common	hypophosphatemia
Nervous System Disorders (SOC)	
Very common	peripheral motor and sensory neuropathy (including hypoaesthesia, paresthesia, dysgeusia, gait disturbance), dizziness
Common	headache
Respiratory, Thoracic and Mediastinal Disorders (SOC)	
Common	pneumonitis
Gastrointestinal Disorders (SOC)	
Very common	nausea, vomiting, diarrhoea, constipation, abdominal pain
Common	dyspepsia
Skin and Subcutaneous Tissue Disorders (SOC)	
Very common	pruritus
Musculoskeletal and connective tissue disorders	
Common	arthralgia
General Disorders and Administration Site Conditions (SOC)	
Very common	fatigue, asthenia, pyrexia, chills
Investigations (SOC)	
Very common	decreased weight
Common	increased lipase, increased transaminase
Injury, poisoning and procedural complications (SOC)	
Very Common	Infusion related reactions[b] (including rash)

[a] ADR associated with fatal outcome
[b] Defined as all adverse events reported as related to study treatment within 24 hours after treatment infusion

Description of selected adverse drug reactions from clinical trials

Myelosuppression
In the pivotal trial, grade 3-4 neutropenia occurred in 56% (27/45) of the patients treated with polatuzumab vedotin plus BR compared to 46% (18/39) of the patients treated with BR only. It led to (any) treatment discontinuation in 11% of patients (5/45) in the polatuzumab vedotin plus BR arm compared to 3% (1/39) of patients in the BR arm.

Grade 3-4 thrombocytopenia occurred in 40% (18/45) of the patients treated with polatuzumab vedotin plus BR compared to 26% (10/39) of the patients treated with BR only. It led to discontinuation of treatment in 11% (5/45) of patients in the polatuzumab vedotin plus BR arm and 5% (2/39) of patients in the BR arm.

Grade 3-4 anaemia occurred in 24% (11/45) of the patients treated with polatuzumab vedotin plus BR compared to 18% (7/39) of the patients treated with BR only. No patients discontinued treatment due to anaemia in either treatment arm.

Peripheral neuropathy (PN)
In the polatuzumab vedotin plus BR arm, Grade 1 PN and Grade 2 PN were reported in 27% and 13% of patients, respectively. In the BR arm, Grade 1 and 2 PN were reported in 3% and 5% of patients, respectively. No Grade 3-5 PN events were reported in either treatment arm. One patient discontinued treatment due to PN and 2 patients had polatuzumab vedotin dose reduction due to PN. No patients in the

BR arm discontinued treatment or had dose reductions due to PN. In the polatuzumab vedotin plus BR arm, the median onset to first event of PN was 1.8 months, and 61% of patients with PN events reported event resolution.

In the whole safety database, grade 3 PN was reported in 19 cases (3%) and grade 4 sensory neuropathy in a single case, which started to resolve after treatment discontinuation.

Infections
Infections, including pneumonia and opportunistic infections (herpetic encephalitis, cerebral toxoplasmosis, cytomegalovirus pneumonia, Pneumocystis jiroveci pneumonia), were reported in approximately half the patients in both treatment arms and were serious in about 30% of the patients in both treatment arms. Fatal infections were reported in 9% of patients in the polatuzumab vedotin plus BR arm and 10% of patients in the BR arm.

Progressive multifocal leukoencephalopathy (PML)
One case of PML, which was fatal, occurred in one patient treated with polatuzumab vedotin plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies.

Hepatic toxicity
In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible.

For more information on the safety of bendamustine and rituximab, please refer to their product information.

4.9 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 an overdose should have immediate interruption of their infusion and be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents; other antineoplastic agents; monoclonal antibodies

ATC code: not yet assigned

Mechanism of action
Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 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 diffuse large B-cell lymphoma. Upon binding to CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Clinical efficacy and safety
The efficacy of polatuzumab vedotin was evaluated in an international, multicentre, open-label study (GO29365) which included a randomised cohort of 80 patients with previously treated DLBCL. Patients were randomized 1:1 to receive polatuzumab vedotin plus bendamustine and rituximab (BR) or BR alone for six 21-day cycles.

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

Polatuzumab vedotin 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 on Day 1 of Cycles 1-6.

The majority of the study population were white (71%) and male (66%). The median age was 69 years (range: 30-86 years). The majority of patients (80%) had ECOG performance score of 0-1. Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% had germinal centre B-cell like (GCB) DLBCL. Primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%) and prior transplant failure (20%). The median number of prior therapies was 2 (range: 1-7), with 29% (n = 23) having received one prior therapy. 80% of patients were refractory to their last anti-lymphoma therapy.

The primary endpoint of the study was complete response (CR) rate at end of treatment as assessed by an Independent Review Committee (IRC). Kaplan-Meier curves for progression-free survival (PFS by Investigator) and overall survival (OS) are shown in Figures 1 and 2, respectively.

Table 4: Summary of efficacy in patients with relapsed/refractory DLBCL from study GO29365

	Polatuzumab vedotin + bendamustine + rituximab N = 40	**Bendamustine + rituximab N = 40**
	Median observation time 22 months	
Primary Endpoint		
Complete Response Rate* (IRC-assessed) at End of treatment**		
Responders (%)	16 (40.0)	7 (17.5)
Difference in response rate (%) [95% CI]	22.5 [2.6, 40.2]	
p-value (CMH chi-squared test***)	0.0261	
Key Endpoints		
Overall Survival		
Number (%) of patients with event	23 (57.5)	28 (70.0)
Median OS (95% CI), months	12.4 (9.0, NE)	4.7 (3.7, 8.3)
HR [95% CI]	0.42 [0.24, 0.75]	
p-value (Log-Rank test, stratified***)	0.0023¶	
Progression Free survival (INV-assessed)		
Number (%) of patients with event	27 (67.5)	35 (87.5)
Median PFS (95% CI), months	7.6 (6.0, 17.0)	2.0 (1.5, 3.7)
HR [95% CI]	0.34 [0.20, 0.57]	
p-value (Log-Rank test, stratified***)	< 0.0001	
Duration of response (INV-assessed) (months)		
Number of patients included in analysis	28	13
Number (%) of patients with event	17 (60.7)	11 (84.6)
Median DOR (95% CI), months	10.3 (5.6, NE)	4.1 (2.6, 12.7)
HR [95% CI]	0.44 [0.20, 0.95]	
p-value (Log-Rank test, stratified***)	0.0321	

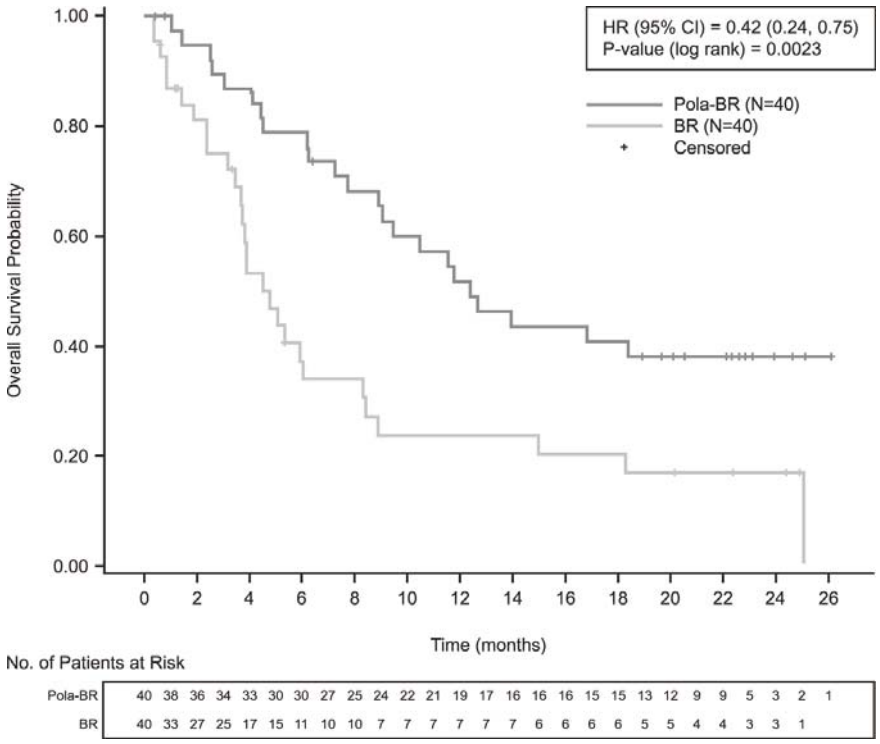
IRC: Independent Review Committee; INV: Investigator; HR: Hazard Ratio; CI: Confidence Interval, NE: Not evaluable; CMH Cochran-Mantel-Haenszel

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

**6-8 weeks after Day 1 of Cycle 6 or last study treatment

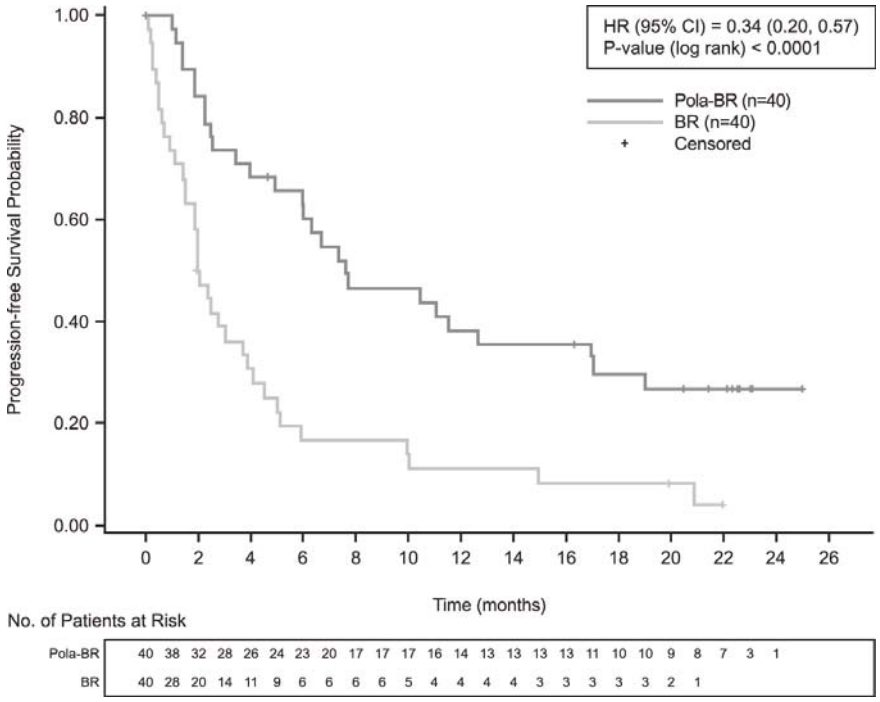
*** Stratification by duration of response to prior therapy (≤ 12 months vs > 12 months)

Figure 1: Kaplan Meier curve of Overall Survival



No: number, Pola: polatuzumab vedotin; BR: bendamustine and rituximab; HR: hazard ratio

Figure 2: Kaplan-Meier curve of investigator-assessed Progression-Free Survival



No: number, Pola: polatuzumab vedotin; BR: bendamustine and rituximab; HR: hazard ratio

Immunogenicity

Across all arms of study GO29365, 8 out of 134 (6%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Across seven clinical studies, 14 out of 536 (3%)

patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Due to this limited number, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

5.2 Pharmacokinetic properties

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

Exposure to 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 Cmax was 6.82 (± 4.73) ng/mL, the time to maximum plasma concentration was approximately 2.5 days, and the terminal half-life was approximately 4 days. Plasma exposures of unconjugated MMAE are < 3% of acMMAE exposures. Based on the population PK analysis there is a decrease of plasma unconjugated MMAE exposure (AUC) after repeated every-three-week dosing.

Based on population pharmacokinetics simulations, a sensitivity analysis predicted exposure to unconjugated MMAE for patients with bodyweight over 100 kg to be increased by 27%.

Distribution
The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume**.** *In vitro*, MMAE is moderately bound (71%-77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells *in vitro*; the blood to plasma ratio is 0.79 to 0.98. *In vitro* data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations.

Biotransformation
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. The levels of MMAE metabolites have not been measured in human plasma.

In vitro studies indicate that MMAE is a substrate for CYP3A4/5 but does not induce major CYP enzymes. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations. MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Elimination
Based on a population PK analysis, the conjugate (acMMAE) is primarily eliminated by non-specific linear time dependent clearance pathway with a value of 0.9 L/day and declines over time. *In vivo* studies in rats dosed with polatuzumab vedotin (radiolabel on MMAE) demonstrate that the majority of radioactivity is excreted in faeces and the minority of radioactivity is excreted in urine.

Elderly
Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on a population PK analysis with patients aged 20-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients < 65 years of age (n = 187) and patients ≥ 65 years of age (n = 273).

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 PK 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.

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

5.3 Preclinical safety data

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

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

No dedicated fertility studies in animals have been performed with polatuzumab vedotin. However, results of repeat dose toxicity in rats indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. In the 4-week repeat-dose toxicity study in rats with weekly dosing of 2, 6, and 10 mg/kg, dose-dependent testicular seminiferous tubule degeneration with abnormal lumen contents in the epididymis was observed. Findings in the testes and epididymis did not reverse and correlated with decreased testes weight and gross findings at recovery necropsy of small and/or soft testes in males given ≥ 2 mg/kg.

No dedicated teratogenicity studies in animals have been performed with polatuzumab vedotin. 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 polatuzumab vedotin every 21-days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid
Sodium hydroxide
Sucrose
Polysorbate 20

6.2 Incompatibilities

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

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

6.3 Shelf life

Unopened vial
60 months when stored at 2 °C to 8 °C.

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

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 72 hours at 2 °C to 8 °C and up to 24 hours at room temperature (9 °C to 25 °C).

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

Acceptable chemical and physical stability of the prepared solution for infusion has been demonstrated for the durations listed in Table 5. Discard diluted polatuzumab vedotin solution if storage time exceeds the limits specified in Table 5.

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]**
Sodium chloride 9 mg/mL (0.9%)	Up to 24 hours at 2 °C to 8 °C or up to 4 hours at room temperature (9 °C to 25 °C)
Sodium chloride 4.5 mg/mL (0.45%)	Up to 72 hours at 2 °C to 8 °C or up to 8 hours at room temperature (9 °C to 25 °C)
5% Glucose	Up to 72 hours at 2 °C to 8 °C or up to 8 hours at room temperature (9 °C to 25 °C)

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Keep vial in the outer carton in order to protect from light.
Do not freeze.
Do not shake.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL vial (Type 1 glass, colourless) with a stopper (fluororesin laminate), with an aluminum seal with plastic flip-off cap, that contains 140 mg active substance polatuzumab vedotin.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

General precautions
Procedures for proper handling and disposal of antineoplastic medicines should be considered.
The reconstituted product contains no preservative and is intended for single-dose only. Proper aseptic technique throughout the handling of this medicinal product should be followed.
Polatuzumab vedotin must be reconstituted using sterile water for injection and diluted into an IV infusion bag containing sodium chloride 9 mg/mL (0.9%), sodium chloride 4.5 mg/ml (0.45%), or 5% glucose prior to administration.
The reconstituted solution and solution for infusion should not be frozen or exposed to direct sunlight.

Instructions for reconstitution

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

Instructions for dilution

1. Polatuzumab vedotin must be diluted to a final concentration of 0.72-2.7 mg/mL in an IV infusion bag, with a minimum volume of 50 mL, containing 9 mg/mL sodium chloride, or 4.5 mg/mL sodium chloride, or 5% glucose.
2. Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose (see below):
   Total PV dose (mL) to be further diluted = $\frac{\text{PV dose (mg/kg) X patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/mL)}}$
3. Using a sterile syringe, withdraw a volume of diluent equivalent to the required volume of reconstituted polatuzumab vedotin from the IV infusion bag.
4. Withdraw the required volume of reconstituted solution from the polatuzumab vedotin vial using a sterile syringe and dilute into the IV infusion bag. Discard any unused portion left in the vial.
5. Gently mix the IV bag by slowly inverting the bag. Do not shake.
6. Inspect the IV bag for particulates and discard if present.

Avoid transportation of the prepared solution for infusion as agitation stress can result in aggregation. If the prepared infusion will be transported, remove air from the infusion bag and limit transportation to 30 minutes at 9°C to 25°C or 2 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.

Polatuzumab vedotin must be administered using a dedicated infusion line equipped with sterile, non-pyrogenic, low protein binding in-line or add-on filter (0.2 or 0.22 micrometer pore size) and catheter.

From a microbiological point of view, the reconstituted solution and the solution for infusion should be used immediately. If not used immediately, the diluted polatuzumab vedotin solution may be stored as specified in section 6.3.

Disposal

Polatuzumab vedotin is for single-dose only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

00031/0010

9. DATE OF SCIENTIFIC OPINION

25 June 2019

Additional information

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm patient eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.polatuzumabeams@roche.com

A Physician Agreement and Safety Data Exchange agreement will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing haematologist/oncologist will also be provided with a physician pack containing all the relevant documents, including the adverse events reporting form, needed to manage patients receiving polatuzumab vedotin under the EAMS.

Contact information

Contact details for reporting Adverse Events/Pregnancies:

SAE Email Address: welwyn.uk_dsc@roche.com

SAE Facsimile Transmission: +44 1707 367582

SAE TELEPHONE CONTACT: +44 1707 367554

Name: UK Drug Safety Centre

Contact email for the EAMS programme (excluding AE reporting):

welwyn.polatuzumabeams@roche.com

Contact Details for Medical Information

Roche Medical Information on 0800 328 1629 or email medinfo.uk@roche.com