Date: 13 October 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Poteligeo

International non-proprietary name: mogamulizumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength: 4 mg/ml
Route(s) of administration: i.v.
Marketing Authorisation Holder: Kyowa Kirin Sàrl
Marketing Authorisation No.: 67444
Decision and Decision date: approved on 01 September 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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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
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
Cmax	Maximum observed plasma/serum concentration of drug
CTCL	Cutaneous T-cell lymphoma
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
ESMO	European Society for Medical Oncology
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Non-proprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MF	Mycosis fungoides
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SS	Sézary syndrome
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)
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 mogamulizumab of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 21 February 2019.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

POTELIGEO is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

2.2.2 Approved Indication

POTELIGEO is indicated for the treatment of adult patients with relapsed of refractory mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy (see section "Clinical Efficacy").

2.2.3 Requested Dosage

The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 September 2020
Formal control completed	7 October 2020
Predecision	7 January 2021
Answers to Predecision	29 March 2021
Final Decision	1 September 2021
Decision	Approval

Swissmedic has not assessed all the primary data of this application and relies for its decision on the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report Poteligeo, Procedure No EMA/H/C/004232/0000, dated 20 September 2018 issued by the EMA.

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3 Medical Context

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common forms of cutaneous T-cell lymphoma (CTCL), a rare, heterogeneous group of mature T-cell lymphomas with primary cutaneous involvement.
In lymphoma classifications, CTCL is considered a subtype of the primary cutaneous lymphomas (PCLs), defined as non-Hodgkin lymphoma that presents in the skin with no evidence of extra-cutaneous disease at diagnosis. MF and SS arise from mature T-cells.
Certain chemokine receptors are upregulated in CTCL that might play a critical role in the migration dynamics of malignant lymphocytes to the skin. The chemokine receptor CCR4 has been associated with skin homing of T cells. CCR4 is overexpressed on the surface of and/or expressed by a high percentage of the cancerous cells in T-cell malignancies such as CTCL.

MF is a disease with a persistent and relapsing course and prognosis is stage dependent. Classic MF is an epidermotropic CTCL clinically characterised by the progression from patch stage to plaques stage and ultimately to tumour stage. MF stages IA or IB have an excellent prognosis; however, progression to advanced stages occurs in around 25% of patients. MF stages IIB and III have a median survival of 4-6 years, and stage IV has a poor prognosis with a median survival of less than 4 years.
SS is a rare, aggressive, leukaemic form of CTCL that is distinguished from MF primarily by the presence of high levels of circulating atypical T cells (Sézary cells), extensive skin erythema and severe pruritus. Both MF and SS are defined histologically and staged by the same criteria. In contrast to patch/plaque MF, SS is much more symptomatic, has lower potential for remission and lower expected survival.

The early stages of MF can be managed with skin direct therapies (e.g. topical steroids, psoralen plus UV-A [PUVA], UV-B, topical cytostatic agents, local electron beam therapy [EBT]). In advanced stages (IIB-IV) and in patients with SS, recommended options include, in combination or alone: total skin EBT, extracorporeal photopheresis (ECP), PUVA, interferon and retinoids.
Low dose methotrexate (not recommended for MF by the ESMO), bexarotene (not licensed in Switzerland), alemtuzumab (not licensed in Switzerland), brentuximab vedotin and multiagent chemotherapy have been recommended for second-line treatment of SS.

Few systemic agents are approved for MF, SS and CTCL in general and the condition often becomes treatment resistant. At present, there are no standard therapies for patients with later stage treatment-resistant disease and there is an unmet medical need.

Mogamulizumab is a defucosylated humanised immunoglobulin G subclass 1 (IgG1) kappa monoclonal antibody that selectively binds to chemokine (C-C motif) receptor 4 (CCR4), a G protein-coupled receptor for C-C chemokines. Mogamulizumab binding to CCR4 directly targets a cell for antibody-dependent cellular cytotoxicity (ADCC) activity.

4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this and relies for its decision on the foreign reference authority, the EMA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Poteligeo, Procedure No EMA/H/C/004232/0000, dated 20 September 2018 issued by the EMA.

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5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and relies for its decision on the foreign reference authority, the EMA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report Poteligeo, Procedure No EMA/H/C/004232/0000, dated 20 September 2018 issued by the EMA.

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6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment report and corresponding product information from the EMA and FDA were used as a basis for the clinical and clinical pharmacology evaluation.
For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, refer to the product information of Poteligeo.

6.1 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 Poteligeo 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 medicinal product 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.

POTELIGEO 4 mg/ml, concentrate for solution for infusion

Composition

Active substances

Mogamulizumabum.

Excipients

Acidum citricum monohydricum, glycinum, polysorbatum 80, natrii hydroxidum (for pH adjustment), acidum hydrochloridum, aqua ad iniectabilia

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
Clear to slightly opalescent, colourless solution.

Each vial contains 20 mg of mogamulizumab in 5 mL, corresponding to 4 mg/mL.

Mogamulizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Indications/Uses

POTELIGEO is indicated for the treatment of adult patients with relapsed of refractory mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy (see section “Clinical Efficacy”).

Dosage/Administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer, and should only be administered by healthcare professionals in an environment where resuscitation equipment is available.

Usual dosage

The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

POTELIGEO should be administered within 2 days of the scheduled day. If a dose is missed by more than 2 days, the next dose should be administered as soon as possible, after which the dosing schedule should be resumed with doses given based on the new scheduled days.

Pre-medication with anti-pyretic and anti-histamine is recommended for the first POTELIGEO infusion. If an infusion reaction occurs, administer pre-medication for subsequent POTELIGEO infusions.

Dose modification

Dermatologic reactions

Patients receiving mogamulizumab have experienced drug rash (drug eruption), some of which were severe and/or serious.

- In the event of a rash (drug related) with severity of Grade 2 or 3 (moderate or severe), treatment with mogamulizumab must be interrupted and the rash should be treated appropriately until rash improves to Grade 1 or less (mild severity), at which time mogamulizumab treatment may be resumed.
- POTELIGEO should be permanently discontinued for a life-threatening (Grade 4) rash (see ”Warnings and precautions”).

Infusion-Related Reactions

- The infusion of POTELIGEO should be temporarily interrupted for mild to severe (Grades 1-3) infusion-related reactions and symptoms treated. The infusion rate should be reduced by at least 50% when re-starting the infusion after symptoms resolve. If reaction recurs, discontinuing the infusion should be considered (see ”Warnings and precautions”).

- POTELIGEO should be permanently discontinued for a life-threatening (Grade 4) infusion-related reaction (see ”Warnings and precautions”).

Special dosage instructions

Children and adolescents

The safety and efficacy of POTELIGEO in children and adolescents aged below 18 years have not been established. No data are available.

Elderly patients

No dose adjustment is required in elderly patients (see ”Pharmacokinetics”).

Patients with impaired renal function

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild to severe renal impairment (see ”Pharmacokinetics”).

Patients with impaired hepatic function

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. POTELIGEO has not been studied in patients with severe hepatic impairment (see ”Pharmacokinetics”).

Mode of administration

POTELIGEO is for intravenous use. It should be administered by intravenous infusion only, over at least 60 minutes. See above recommendations in case of infusion-related reaction.

For instructions on the dilution of the medicinal product before administration, see ”Other information”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in ”Composition”.

Warnings and precautions

Dermatologic Reactions

Patients receiving mogamulizumab have experienced drug rash (drug eruption), some of which were severe and/or serious.

When mogamulizumab has been administered to patients with T-cell lymphomas other than MF or SS, serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in less than 1% of patients during clinical trials, and also reported during the post-marketing period; some of these cases were reported with fatal outcomes. Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, POTELIGEO should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less. If SJS/TEN occur, appropriate medical therapy should be administered. See ”Dosage/Administration” for dose modification information.

Infusion-related reactions

Acute infusion-related reactions (IRRs) have been observed in patients treated with mogamulizumab. The IRRs were mostly mild or moderate in severity, although there have been a few reports of severe reactions (Grade 3). The majority of IRRs occur during or shortly after the first infusion (all within 24 hours of administration), with the incidence decreasing over subsequent treatments.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of mogamulizumab should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. See ”Dosage/Administration” for pre-medication and dose modification information.

Infections

Subjects with MF or SS treated with mogamulizumab are at increased risk of serious infection and/or viral reactivation. The combination of mogamulizumab with systemic immune modulating medicinal products or with other licensed therapies for MF or SS has not been studied and is, therefore, not recommended, especially in consideration of the risk of severe infections in patients treated with mogamulizumab. Topical steroids or low doses of systemic corticosteroids may be used during treatment with mogamulizumab; however, the risk of serious infection and/or viral reactivation may be

higher in case of concomitant administration with systemic immunosuppressive agents. Patients should be monitored for signs and symptoms of infection and treated promptly.

Patients should be tested for hepatitis B infection before initiating treatment with mogamulizumab. For patients who test positive for current/previous hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended for advice concerning appropriate measures against hepatitis B reactivation.

Complications of allogeneic hematopoietic stem cell transplantation (HSCT) after mogamulizumab

Complications, including severe graft versus host disease (GVHD), have been reported in patients with T-cell lymphomas other than MF or SS who received allogeneic HSCT after mogamulizumab.

A higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

The safety of treatment with mogamulizumab after autologous or allogeneic HSCT has not been studied.

Tumor lysis syndrome

Tumour lysis syndrome (TLS) has been observed in patients receiving mogamulizumab. TLS was observed most frequently during the first month of treatment. Patients with rapidly proliferating tumour and high tumour burden are at risk of TLS. Patients should be monitored closely by appropriate laboratory and clinical tests for electrolyte status, hydration and renal function, particularly in the first month of treatment, and managed according to best medical practice. Management of TLS may include aggressive hydration, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care

Cardiac Disorders

One case of acute myocardial infarction has been observed in a clinical trial patient with MF/SS receiving mogamulizumab. In clinical trial patients with other T-cell lymphomas there have been reports of stress cardiomyopathy (one case) and acute myocardial infarction (one case). The subjects had a medical history including various risk factors. Patients who have risk factors associated with cardiac disease should be monitored and appropriate precautions taken.

Large cell transformation (LCT)

There are limited data available on patients with LCT.

Other

Mogamulizumab should not be administered subcutaneously or intramuscularly, by rapid intravenous administration, or as an intravenous bolus.

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

Interactions

No interaction studies have been performed.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential and males of reproductive potential should use effective contraception during treatment with POTELIGEO and for at least 6 months after treatment .

Pregnancy

There are no data from the use of mogamulizumab in pregnant women. Although mogamulizumab crosses the placental barrier in animals, apart from the pharmacological effect in foetuses, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see ”Preclinical data”). As a precautionary measure, it is preferable to avoid the use of mogamulizumab during pregnancy.

Lactation

It is unknown whether mogamulizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards POTELIGEO could be used during breast-feeding if clinically needed.

Fertility

There are no clinical data available on the effect of mogamulizumab on human fertility. No adverse effects on male and female reproductive organs were observed in animal studies (see ”Preclinical data”).

Effects on ability to drive and use machines

Mogamulizumab has minor influence on the ability to drive and use machines. Patients should be advised that fatigue, nausea or vomiting may occur during treatment with Poteligeo. Patients should be advised not to drive or operate machinery if they experience such side effects.

Undesirable effects

Summary of the safety profile

The most frequently reported undesirable effects were infusion-related reaction (30.0%) and rash (drug eruption) (21.5%); most of these effects were non-serious and Grades 1 or 2.
Severe adverse reactions included Grade 4 respiratory failure (0.9%) and Grade 5 reactions were polymyositis and sepsis (0.4% each).
The most frequently reported serious adverse reactions were pneumonia and pyrexia (1.7% each), and infusion-related reaction and cellulitis (1.3% each).

Tabulated list of undesirable effects

The undesirable effects are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions occurring in patients receiving POTELIGEO (N=233)

System Organ Class (SOC)	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	Common	Anaemia, neutropenia, leukopenia, thrombocytopenia, lymphocyte count decreased
Endocrine disorders	Common	Hypothyroidism
Gastrointestinal disorders	Very common	Constipation (9.9%), diarrhoea (20.6%) nausea (18.0%)
	Common	Vomiting, stomatitis

General disorders and administration site conditions	Very common	Fatigue (21.5%), oedema peripheral (10.7%), pyrexia (17.6%)
Hepatobiliary disorders	Uncommon	Hepatitis acute, hepatitis
	Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Infections and infestations	Very common	Infections (64.8%)[a]
	Common	Upper respiratory tract infection
Injury, poisoning and procedural complications	Very common	Infusion related reaction (30.0%)
Metabolism and nutrition disorders	Uncommon	Tumour lysis syndrome
Nervous system disorders	Very common	Headache (14.2%)
Skin and subcutaneous tissue disorders	Very common	Drug eruption (including skin rash) (21.5%)

[a] Folliculitis, cellulitis, candidiasis, pneumonia, sepsis, skin infection, otitis externa, herpes zoster, staphylococcal skin infection, urinary tract infection, herpes simplex and cytomegalovirus

Description of selected undesirable effects

Dermatologic reactions

Patients receiving POTELIGEO have experienced drug rash (drug eruption). The majority of treatment-related dermatologic reactions were Grade 1 or 2 (91%).
Grade ≥3 drug rash occurred in 4.3% of all patients. No trend in latency to event onset was identified for drug eruptions and rashes; both early and late-onset events occurred.

Infusion-related reactions[34,]

Infusion-related reactions have been observed in 30% of patients treated with POTELIGEO. The majority (95%) of treatment-related infusion-related reactions were Grade 1 or 2 and occurred during or shortly after the first infusion.
Severe reactions (Grade 3) were experienced by 1.3% of all patients.

The incidence of infusion-related reactions was highest after the first infusion (28.8% of subjects), reducing to ≤ 3.8% of subjects after two or more infusions.

Infusion interruptions occurred in approximately 6% of patients, most of which (approximately 90%) occurred within the first cycle of treatment with mogamulizumab.

Less than 1% of patients treated in Study 0761-010 discontinued treatment due to infusion-related reactions.

Serious infections

Patients with MF or SS are at increased risk of serious infection due to the disruption of dermal integrity caused by cutaneous disease, as well as the immunosuppressive effects of extracutaneous disease, and treatment with mogamulizumab may increase that risk. Serious infections, including sepsis, pneumonia and skin infections, were experienced by 14.6% of subjects receiving mogamulizumab. The latency to event onset following the first dose varied considerably. The majority of infections (89.8%) were resolved. In the clinical trial (0761-010), there were 2 reports of respiratory failure with fatal outcome in patients with severe pneumonia occurring more than 9 months after starting treatment with mogamulizumab.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. A small percentage (3.9%) of patients receiving POTELIGEO tested positive for treatment emergent (treatment induced or treatment boosted) anti mogamulizumab antibodies. There were no positive neutralising antibody responses.

Safety post last dose

Of the 320 subjects exposed to mogamulizumab in Study 0761-010, 21 (6.6%) experienced at least one serious adverse drug reaction (SADR) that occurred within 90 days from the date of last study drug administration.

Of these, SADRs that were reported in more than one patient were coded under the SOCs Infections and infestations (7 [2.2%] patients), General disorders and administration site conditions (5 [1.6%] patients), Respiratory, thoracic and mediastinal disorders (4 [1.3%] patients), Musculoskeletal and connective tissue disorders (3 [0.9%] patients), Hepatobiliary disorders (2 [0.6%] patients), and Injury, poisoning and procedural complications (2 [0.6%] patients). All remaining SOCs reported SADRs in one patient (0.3%).

The safety profile observed in the 90 days following the last dose of mogamulizumab is consistent with the safety profile observed during the study treatment period.

Elderly patients

The safety profile in elderly patients (≥ 65 years) was generally consistent with that of adult patients, except for dermatologic reactions (54.5%) and infusion related reactions (33.3%) which were seen more often in older subjects.

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 information on overdose with mogamulizumab. In case of overdose, the patient, including their vital signs, should be closely monitored (for at least 1 hour) and supportive treatment should be administered if required.

Properties/Effects

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents (monoclonal antibodies)

ATC code

L01XC25

Mechanism of action/ Pharmacodynamics

Mogamulizumab is a defucosylated, humanised IgG1 kappa immunoglobulin that selectively binds to CCR4, a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells. CCR4 is expressed on the surface of some cancer cells including T cell malignancies, such as as MF and SS in which CCR4 expression is inherent.

Clinical efficacy

The efficacy of mogamulizumab in the treatment of patients with mycosis fungoides (MF) or Sézary syndrome (SS) was established in a Phase 3, multicentre, open-label, study (0761-010) of 372 adult patients randomised 1:1 to treatment with either mogamulizumab or vorinostat. Each arm enrolled 186 patients. Mogamulizumab infusion was administered at a dose of 1 mg/kg once weekly for the first 28-day cycle (on Days 1, 8, 15 and 22), and on days 1 and 15 of subsequent 28-day cycles. Vorinostat was administered at a starting dose of 400 mg orally, once daily beginning on day 1 for 28-

day cycles. Vorinostat patients with disease progression or unacceptable toxicities were permitted to cross over to mogamulizumab therapy. Crossover patients received up to 46 months of mogamulizumab therapy, as of December 2016 data cut. Treatment with mogamulizumab continued until disease progression or unacceptable toxicity. The trial excluded patients with active autoimmune diseases, central nervous system metastasis, and medical conditions that required systemic corticosteroids or other immunosuppressive medicinal products, or an active infection requiring therapy, including HIV, or hepatitis B or C. Patients with ECOG performance status ≥2 were also excluded. At study baseline, 38% had stage IB-II disease, 10% stage III, 52% stage IV. This study included patients regardless of their baseline level of CCR4 expression in skin biopsy.

The primary efficacy endpoint was progression-free survival (PFS) based on investigator assessment using a global composite response criteria that took into account all potentially affected disease compartments (skin, blood, lymph nodes and viscera).

All patients had a histologically confirmed diagnosis of mycosis fungoides (MF), 56.5%, 53.2%, or Sézary Syndrome (SS), 43.5%, 46.8%, in the mogamulizumab and vorinostat groups, respectively, and had received at least one prior systemic therapy. The most common prior systemic therapies used by subjects in Europe were bexarotene (70%), interferon (59%), methotrexate (49%), extracorporeal photopheresis (ECP) (31%) and gemcitabine/gemcitabine regimens (28%).

The median duration of exposure with mogamulizumab was 5.6 months (range: <1 to 45.3 months). 56% of patients received mogamulizumab for at least 6 cycles, and 25% of patients received mogamulizumab for at least 12 cycles.

Patients were a median age of 64 years at the time of screening (range 25 to 101 years), 49.5% were 65 years or older, and 58.1% were male.

CCR4 expression was assessed retrospectively on pretreatment skin biopsies (formalin fixed paraffin embedded) using immunohistochemistry. In the mogamulizumab arm, baseline CCR4 expression levels were available in 75% of patients (N=140). CCR4 was detected on ≥1% of lymphocytes in 100% of patients, and 96% (134/140) had CCR4 detected on ≥10% of skin lymphocytes.

Of the patients randomised to vorinostat, 136 patients (73.1%) crossed over to mogamulizumab during the study. Reasons for crossover to mogamulizumab were disease progression (109 patients) and treatment intolerance (27 patients) .

Median PFS for the mogamulizumab group was 7.7 months (95% CI: 5.67, 10.33) and 3.1 months (95% CI: 2.87, 4.07) for the vorinostat group with resultant hazard ration of 0.53 (95% CI: 0.41, 0.69), p<0.0001 (2-sided, stratified log rank test). At 6, 12, 18 and 24 months after the start of randomised treatment, the percent of subjects alive without disease progression was higher for mogamulizumab (55.3%, 38.3%, 28.0%, and 14.1%, respectively) compared to vorinostat (28.8%, 15.3%, 7.2%, and 7.2%, respectively).

Key secondary endpoints were overall response rate (ORR), ORR after crossover and duration of response (DOR).

Overall response was reported as a composite score from measures in each compartment, and a response had to be demonstrated at two successive overall disease assessments in order to be confirmed..

Table 2 summarises ORR and DOR, and response by compartment. Response in the viscera could not be evaluated due to limited efficacy data in subjects with visceral involvement; the benefit-risk of mogamulizumab in subjects with visceral involvement is currently undetermined due to lack of data.

Table 2: Response during randomised treatment period in study 0761-010 (intent-to-treat)

	Mogamulizumab N=186	**Vorinostat N=186**
Overall response rate (confirmed CR + PR, %)	28.0	4.8
95% CI	(21.6, 35.0)	(2.2, 9.0)
P-value[a]	<.0001	
Duration of response (months)		
Median (95% CI)	14.1 (9.4, 19.2)	9.13 (4.7,-)
Response by compartment		
Blood	n=124	n=125
Response rate (confirmed CR + PR, %)	66.9	18.4
95% CI	(57.9, 75.1)	(12.0, 26.3)
P-value[a]	<0.0001	
Skin	n=186	n=186
Overall response rate (confirmed CR + PR, %)	41.9	15.6
95% CI	(34.8, 49.4)	(10.7, 21.6)
P-value[a]	<0.0001	
Lymph nodes	n=136	n=133

Overall response rate (confirmed CR + PR, %)	15.4	3.8
95% CI	(9.8, 22.6)	(1.2, 8.6)
P-value[a]	0.0008	
Viscera	n=6	n=4
Overall response rate (confirmed CR + PR, %)	0	0
95% CI	(0.0, 45.9)	0.0, 60.2)

Note: Overall response rate is based on Global Composite Response score.

[a]: P-value was obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region.

CI=confidence interval; CR=complete response; PR=partial response

There are limited efficacy data in patients with low (<10%) CCR4 expression in the skin. In Study 0761-010 there were 10/290 evaluable patients with CCR4 expression <10%, of which 6 were randomised to mogamulizumab, and 4 were randomised to vorinostat and subsequently crossed over to mogamulizumab. No confirmed responses were observed in these 10 subjects with low (<10%) CCR4 expression.

Patients with stage IB/II disease treated with mogamulizumab had confirmed ORR of 17.6% compared to 8.3% for vorinostat, and compartment level (blood, skin, lymph node) response rates that were higher than those for vorinostat treated patients. Overall, the median period of progression free survival for stage IB/II subjects treated with mogamulizumab was 4.7 months compared to 3.9 months for vorinostat-treated patients. In patients with stage IB/II disease, given the limited number of subjects with a response and immaturity of the data, no conclusion on duration of response can be made.

Time to compartment level response in Stage IB/II patients was approximately 3 months, which is consistent with time to response for the ITT population overall (approximately 3 months). If a compartment level response or overall response is not observed after 3 months of treatment, discontinuation of treatment should be considered.

Children and adolescents

Swissmedic has accepted an exemption for this medicinal product from the obligation to submit results on paediatric studies in all subsets of the paediatric population in the treatment of cutaneous T-cell lymphoma (CTCL) (MF and SS are subtypes of CTCL).

Pharmacokinetics

The pharmacokinetics (PK) of mogamulizumab was evaluated in adult patients with T-cell leukaemia-lymphoma (ATL) and CTCL over a dose range of 0.01 to 1 mg/kg administered as multiple doses of mogamulizumab every week or every 2 weeks, and included the recommended 1.0 mg/kg dose and regimen (days 1, 8, 15 and 22 for the first 28-day cycle and on Days 1 and 15 for subsequent 28-day cycles). The population PK analysis included 444 patients receiving mogamulizumab in six clinical trials. The exposure to mogamulizumab increased proportionally with dose over the dose range of 0.1 to 1.0 mg/kg.

Absorption

Mogamulizumab is dosed via intravenous route and therefore is immediately and completely bioavailable.

Distribution

Based on a population PK analysis, the geometric mean [% coefficient of variation (CV%)] central volume of distribution (Vc) was 3.57 L (20.1%).

Metabolism

The metabolic pathway of mogamulizumab has not been characterised. Mogamulizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Based on a population PK analysis, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 12.0 mL/h (83.7%) and geometric mean elimination half-life ($t_{1/2}$) is 17 days (65.5%).

Linearity and accumulation

Mogamulizumab exhibits linear PK from the dose in a dose range of 0.01 mg/kg to 1 mg/kg. Based on a population PK analysis, the steady-state concentrations of mogamulizumab were reached after 12 weeks of repeated dosing when administered using the recommended regimen, and systemic accumulation was 1.7-fold. On a power model analysis, no deviation from dose proportionality was evident.

Kinetics in specific patient groups

Renal impairment

The effect of renal impairment on the clearance of mogamulizumab was evaluated by a population PK analysis in patients with mild (creatinine clearance [CrCL] between 60 and 89; n= 157), moderate (CrCL between 59 and 30; n= 80), or severe renal impairment (CrCL less than 30 mL/min; n= 2). No clinically important differences in the clearance of mogamulizumab were found between patients with mild to severe renal impairment and patients with normal renal function.

Hepatic impairment

The effect of hepatic impairment on the clearance of mogamulizumab was evaluated by a population PK analysis in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n= 80) or moderate (TB greater than 1.5 to 3 times ULN and any AST; n=3) hepatic impairment. No clinically important differences in the clearance of mogamulizumab were found between patients with mild to moderate hepatic impairment and patients with normal hepatic function. Mogamulizumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

Other special populations

The effects of various covariates on the PK s of mogamulizumab were assessed in population PK analyses. The following factors had no clinically important effect on the CL of mogamulizumab: age (range: 22 to 101 years), sex, ethnicity (other than Japanese, limited data are available in other ethnic populations), renal impairment, mild or moderate hepatic impairment, disease subtype (mycosis fungoides (MF) or Sézary Syndrome (SS)), degree of CCR4 expression or ECOG status, although it should be noted that patients with ECOG PS ≥2 were excluded from the clinical trials.

Pharmacokinetic/pharmacodynamics relationship(s)

Efficacy

Exposure-Response analysis indicated that efficacy was not correlated with mogamulizumab exposure in the pivotal study. Efficacy, as measured by improvement in PFS based on investigator assessment, was not associated with increasing mogamulizumab exposure.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity.

Mutagenicity / Carcinogenicity

Genotoxicity or Carcinogenicity studies have not been conducted with mogamulizumab.

Reproductive toxicity

In an animal reproductive and developmental toxicity study, administration of mogamulizumab to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for embryo-foetal lethality, teratogenicity, or foetal growth retardation. In general, IgG molecules are known to cross the placental barrier and mogamulizumab concentrations in foetus plasma were detected. Pharmacological activity of mogamulizumab was noted in foetuses as was evident from a decrease in CCR4 expressing lymphocytes.
No specific studies have been conducted to evaluate potential effects on fertility. No mogamulizumab-related toxic effects in the male and female reproductive organs were observed in repeat-dose toxicology studies in sexually mature monkeys up to 26 weeks.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Mogamulizumab should not be infused concomitantly in the same intravenous line with other medicinal products.

Effects on diagnostic methods

Not applicable.

Shelf life

Do not use this medicine after the expiry date (”EXP”) stated on the pack.

Shelf life after opening

POTELIGEO does not contain a preservative. Once opened, the medicinal product should be diluted and infused immediately (see ”Instructions for handling”).

After preparation of infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (at 25°C) under ambient room light.

These time limits include storage of the infusion solution in the infusion bag through the duration of infusion. From a microbiological point of view, the product must be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 4 hours at 2°C - 8°C provided that dilution has taken place under controlled and validated aseptic conditions.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

For storage conditions after dilution of the medicinal product, see ”After preparation of infusion”.

Instructions for handling

Preparation

- Visually inspect the medicinal product for particulate matter and discolouration prior to administration. POTELIGEO is a clear to slightly opalescent, colourless solution. Discard the vial if cloudiness, discolouration or particulates are observed.
- Calculate the required volume of POTELIGEO needed to prepare the infusion solution for the 1 mg/kg dosage based on patient weight (see section ”Dosage/administration”). Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an infusion bag containing 9mg per ml (0.9%) sodium chloride solution for injection. Mix diluted solution by gentle inversion. Do not shake. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Each vial is for single use only. Discard any unused portion left in the vial in accordance with local requirements.

Administration

- The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.
- Do not mix POTELIGEO with, or administer as an infusion with, other medicinal products.
- POTELIGEO is intended for intravenous use only, and should not be administered subcutaneously, intramuscularly, as a bolus dose or by rapid intravenous administration.
- Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding 0.22 micron (or equivalent) in-line filter.

Authorisation number

67444 (Swissmedic)

Packs

5 mL solution in 10 mL glass vial (type I glass) with a rubber stopper, an aluminum seal and a polypropylene flip-off cap.

Pack of 1 vial [A].
To be used in hospitals only.

Marketing authorisation holder

Kyowa Kirin Sàrl, Genève.

Date of revision of the text

September 2021