Celgene | Bristol Myers Squibb™ Company

ZEPOSIA®

0,23 mg, 0,46 mg, 0,92 mg hard-capsules

Swiss Summary of the Risk Management Plan (RMP) for ZEPOSIA® (Ozanimod)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of ZEPOSIA is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of ZEPOSIA in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Celgene GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of ZEPOSIA.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR ZEPOSIA

This is a summary of the risk management plan (RMP) for Zeposia. The RMP details important risks of Zeposia, how these risks can be minimised, and how more information will be obtained about Zeposia's risks and uncertainties (missing information).

Zeposia's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zeposia should be used.

This summary of the RMP for Zeposia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zeposia's RMP.

1.1. The Medicine and what it is Used for

Zeposia is authorised for the treatment of adult patients with relapsing remitting multiple sclerosis (MS) with active disease (see SmPC for the full indication). It contains ozanimod as the active substance and it is given by oral route of administration.

Further information about the evaluation of Zeposia's benefits can be found in Zeposia's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/zeposia.

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zeposia, together with measures to minimise such risks and the proposed studies for learning more about Zeposia's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Zeposia, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zeposia is not yet available, it is listed under ‘missing information’ below.

1.3. List of Important Risks and Missing Information

Important risks of Zeposia are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zeposia. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Important identified and potential risks, together with missing information, are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks	• None
Important Potential Risks	• Symptomatic slow heart rate (HR; symptomatic bradycardia) • Severe liver injury • Serious infection in patients with weakened immune systems (serious opportunistic infections including PML) • Swelling of a part of the retina (macular oedema) • Cancer (malignancy) • Syndrome characterised by headache, confusion, seizures and visual loss (posterior reversible encephalopathy syndrome; PRES) • Toxicity to unborn child in women who have received treatment with ozanimod (embryofoetal toxicity in exposed pregnant females)
Missing Information	• Heart problems that develop following long-term treatment with ozanimod (long-term cardiovascular effects) • Effects following withdrawal of drug • Use in patients over 55 years

1.4. Summary of Important Risks

Table 2: Symptomatic Slow Heart Rate (Symptomatic Bradycardia)

Important Potential Risk: Symptomatic Slow Heart Rate (Symptomatic Bradycardia)	
Evidence for linking the risk to the medicine	Initiation of ozanimod may result in transient reductions in HR. A dose escalation schedule (0.23 mg ozanimod followed by 0.46 mg and 0.92 mg) attenuates the magnitude of HR reductions. Initiation of ozanimod without dose escalation may result in greater reductions in HR. In active-controlled MS clinical trials, after the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in HR of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. Heart rates below 40 bpm were not observed. Initiation of ozanimod without dose escalation may result in greater reductions in HR. With the use of a dose

Table 2: Symptomatic Slow Heart Rate (Symptomatic Bradycardia) (Continued)

Important Potential Risk: Symptomatic Slow Heart Rate (Symptomatic Bradycardia)	
Evidence for linking the risk to the medicine (Continued)	escalation regimen over the first 7 days of treatment initiation, there has only been one case of confirmed symptomatic bradycardia observed in active-controlled Phase 3 MS studies (Pool A1). This patient, with a pretreatment HR of 48 bpm experienced mild dizziness at Hour 6 on Day 1, in the presence of a HR of 47 bpm. The dizziness resolved after a single dose of atropine although HR remained at 44 bpm. It is likely that pre-existing dysautonomia contributed to the patient's bradycardia and blunted the HR response to atropine. The patient continued ozanimod treatment uneventfully. In Pool B, one further event of nonserious symptomatic bradycardia was reported in one patient commencing 0.23 mg ozanimod. The patient experienced dizziness and sleepiness, with a lowest HR of 46 bpm at Hour 4. The event did not lead to dose modification or discontinuation.
Risk factors and risk groups	Symptomatic bradycardia is a rare occurrence and has not been of clinical consequence. The administration of ozanimod in patients on both a beta blocker and a calcium channel blocker has not been studied. Any reports of symptoms in patients receiving these drugs concurrently in clinical practice will be analysed.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. PL Sections 2, 3 and 4. Ozanimod is contraindicated in patients at risk of symptomatic bradycardia (SmPC Section 4.3, PL Section 2). Initial dose escalation regimen for ozanimod and advice regarding re-initiation of therapy following treatment interruption is described in SmPC Section 4.2 and PL Section 3. Recommendation that an ECG in all patients should be obtained prior to treatment initiation with ozanimod to determine whether any pre-existing cardiac abnormalities are present is included in SmPC Section 4.4 and PL Section 2. Warning that ozanimod may result in transient reductions in HR is included in SmPC Sections 4.4 and 5.1. Initiation pack covering dosing for the first 7 days, or in the case of resuming treatment following treatment interruption. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	ORION study. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 3: Severe Liver Injury

Important Potential Risk: Severe Liver Injury	
Evidence for linking the risk to the medicine	Severe drug-induced liver injury (DILI) is considered to be of public health concern. In the case of ozanimod, the majority of liver-related events (predominately alanine aminotransferase [ALT] and gamma glutamyltransferase [GGT] elevations) were mild to moderate in intensity and resolved while continuing treatment. In active-controlled MS clinical trials, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on interferon (IFN) β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ozanimod 0.92 mg and 3.1% of patients on IFN β-1a. When elevations in hepatic tests occurred, they were generally asymptomatic. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3-fold the ULN within approximately 2 to 4 weeks. In active-controlled MS clinical trials, ozanimod was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of patients on ozanimod 0.92 mg and 0.8% of patients on IFN β-1a. Although there have been instances (5/1774 [0.28%] patients in Pool A1) where observations of ALT or aspartate aminotransferase were ≥ 3-fold the ULN together with bilirubin > 2-fold the ULN in clinical trials, no cases of severe DILI (confirmed Hy's Law cases) were observed with ozanimod.
Risk factors and risk groups	Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod. However, it is not known whether these patients are at increased risk of severe liver injury.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe hepatic impairment (SmPC Section 4.3, PL Section 2). Recommendations to measure transaminase and bilirubin levels before treatment initiation, for liver function monitoring and treatment discontinuation if significant liver injury is confirmed, are included in SmPC Section 4.4 and PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 4: Serious Infections in Patients with Weakened Immune Systems (Serious Opportunistic Infections Including PML)

Important Potential Risk: Serious Infections in Patients with Weakened Immune Systems (Serious Opportunistic Infections Including PML)	
Evidence for linking the risk to the medicine	No cases of serious opportunistic infection, including PML, were observed with ozanimod in the active-controlled MS clinical trials. However, ozanimod clinical development exposure is insufficient to exclude the risk of PML.
Risk factors and risk groups	Patients with prolonged and profound lymphopaenia may be at increased risk of developing severe opportunistic infection, including PML, and also those who have received previous natalizumab treatment, although the risks appear to be very low.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, and 4.8. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe active infections, active chronic infections such as hepatitis and tuberculosis (SmPC Section 4.3). Recommendation that discontinuation of ozanimod be considered in case of opportunistic infection is included in SmPC Section 4.4. Recommendations to measure blood cell counts prior to and during treatment with ozanimod, advice to monitor patients at risk of infection, clinical symptoms or MRI findings that physicians should be vigilant for as suggestive of PML, treatment instructions in cases suggestive of PML and treatment discontinuation if PML is confirmed are provided in SmPC Section 4.4 and PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	ORION study.[a] Long-term follow-up of Study RPC01-3001.[a] See Section 1.5 of this summary for an overview of the postauthorisation development plan.

[a] Note ORION and long-term follow-up of Study RPC01-3001 are not powered to assess PML

Table 5: Swelling of a Part of the Retina (Macular Oedema)

Important Potential Risk: Swelling of a Part of the Retina (Macular Oedema)	
Evidence for linking the risk to the medicine	In Pool A1 there were three confirmed cases in the ozanimod 0.46 mg group, one confirmed case in the ozanimod 0.92 mg group and none in the IFN β-1a treatment group. In Pool B, there were three additional confirmed cases in the extension study RPC01-3001 (ozanimod 0.92 mg). Following adjudication by a panel of ophthalmology experts including two neuro-ophthalmologists and a retinal specialist, all seven cases were confounded by pre-existing risk factors including a history of macular oedema, uveitis, other ocular inflammation, or trauma. In one case, drug was continued with recovery. In the remaining six cases, upon drug discontinuation, five cases showed full recovery and the case with trauma was stable.

Table 5: Swelling of a Part of the Retina (Macular Oedema) (Continued)

Important Potential Risk: Swelling of a Part of the Retina (Macular Oedema)	
Risk factors and risk groups	Patients with risk factors for macular oedema such as a history of uveitis or diabetes mellitus.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Recommendations for treatment of patients with risk factors for macular oedema (SmPC Section 4.4. and PL Section 2) and treatment discontinuation if significant macular oedema is confirmed are described in SmPC Section 4.4. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 6: Cancer (Malignancy)

Important Potential Risk: Cancer (Malignancy)	
Evidence for linking the risk to the medicine	In Pool A1, there were 4 treatment-emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 4 NMSCs versus 1 and 1 for IFN, respectively. In Pool B, there were 12 treatment-emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 9 NMSCs versus 1 and 1 for IFN, respectively. Incidence rates of malignancies for ozanimod were within background rates in age matched MS and general populations.
Risk factors and risk groups	Risk factors for malignancies are not fully understood. Risk factors known to cause cancer include advancing age, and lifestyle (such as smoking, alcohol, certain infections, lack of physical activities, poor diet, obesity, excessive exposure to the sun or other radiation, exposure to chemicals or hormone replacement). Some genes such as BRCA are known to cause cancers (breast, ovarian and prostate). However, it is not known what proportion of cancer is caused by faulty genes. Patients who are profoundly immunosuppressed are also at increased risk of developing malignancy, typically lymphomas. Chronic inflammatory conditions may also increase the risk of cancer. Many cancers develop as a result of combination of genetics, environmental factors and lifestyle.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2 Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3, PL Section 2). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous immunosuppressive therapy, is included in SmPC Section 4.4. Recommendation that patients treated with ozanimod should be cautioned against exposure to sunlight without protection. Warning that patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy (SmPC Section 4.4, PL Section 2).

Table 6: Cancer (Malignancy) (Continued)

Important Potential Risk: Cancer (Malignancy)	
Risk minimisation measures (Continued)	**Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 7: Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome)

Important Potential Risk: Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome)	
Evidence for linking the risk to the medicine	In controlled clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome.
Risk factors and risk groups	Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension and may be predisposing factors. Radiologically, extensive bilateral white matter abnormalities suggestive of oedema in the posterior regions of cerebral hemispheres were seen in a variety of conditions (Pavlakis, 1999; Legriel, 2011), including severe hypertension, uraemia, toxaemia of pregnancy, use of immunosuppressive drugs (ie, cyclosporine A) and cytotoxic agents, including alkylating agents, antimetabolites, mitotic inhibitors, antiangiogenic agents and antitumour necrosis factor alpha agents, granulocyte colony-stimulating factor and erythropoietin. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES. Patients with renal dysfunction appear to be at higher risk of developing PRES despite only moderate acute elevation of their blood pressure (Ay, 1998). In patients with PRES associated renal disease treated with antihypertensive medications, neurological deficits resolved within 2 weeks (Hinchey, 1996). PRES can manifest with acute seizures without an obvious prodrome. These patients become seizure free after resolution of the imaging abnormalities and they do not require long-term antiepileptic therapy (Bakshi, 1998; Hauser, 1988). PRES in the setting of autonomic dysfunction may also be a complication of Guillain-Barré syndrome (Nabi, 2016; Chen, 2015).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2 Recommendation to discontinue ozanimod if PRES is suspected is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.

Table 7: Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome) (Continued)

Important Potential Risk: Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome)	
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 8: Toxicity to Unborn Child in Women who have Received Treatment with Ozanimod (Embryofoetal Toxicity in Exposed Pregnant Females)

Important Potential Risk: Toxicity to Unborn Child in Women who have Received Treatment with Ozanimod (Embryofoetal Toxicity in Exposed Pregnant Females)	
Evidence for linking the risk to the medicine	A total of 33 pregnancies and 10 partner pregnancies have been reported in the safety database in patients treated with ozanimod across all indications. Oral contraception or intrauterine device was used in 11/33 patient pregnancies. Potentially less effective methods were employed in the remainder. There were 28 cases of pregnancies in female patients with relapsing MS who were treated with ozanimod. Embryofoetal toxicity in exposed pregnant females is considered to be an important potential risk due to findings in animal studies. Clinical trial patients were instructed to avoid pregnancy during the trials and for a period after discontinuing medication as specified in the protocol, and to immediately discontinue study medication if pregnancy were diagnosed. All exposures occurred during the first trimester of pregnancy.
Risk factors and risk groups	No specific risk groups or risk factors have been identified.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.6 and 5.3. PL Section 2 Advice for women of childbearing potential to use effective contraception during treatment, and for at least 3 months after ozanimod treatment discontinuation is included in SmPC Sections 4.4 and 4.6, and PL Section 2. Ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception, a negative pregnancy test must be available in women of childbearing potential before starting treatment, and counselling information regarding the serious risk to the foetus (SmPC Sections 4.4 and 4.6, and PL Section 2) and ultrasonography examinations should be provided (SmPC Section 4.6 and PL Section 2). Instruction not to use ozanimod during pregnancy, or in women of childbearing potential not using effective contraception, and advice for women of childbearing potential, are provided in PL Section 2. If a woman becomes pregnant during treatment, treatment should be discontinued, and the woman should receive pre-natal monitoring (SmPC Section 4.6 and PL Section 2).

Table 8: Toxicity to Unborn Child in Women who have Received Treatment with Ozanimod (Embryofoetal Toxicity in Exposed Pregnant Females) (Continued)

Important Potential Risk: Toxicity to Unborn Child in Women who have Received Treatment with Ozanimod (Embryofoetal Toxicity in Exposed Pregnant Females)	
Risk minimisation measures (Continued)	**Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide – Pregnancy-specific patient reminder card.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 9: Heart Problems that Develop Following Long-term Treatment with Ozanimod (Long-term Cardiovascular Effects)

Missing Information: Heart Problems that Develop Following Long-term Treatment with Ozanimod (Long-term Cardiovascular Effects)	
Risk minimisation measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 10: Effects Following Withdrawal of Drug

Missing Information: Effects Following Withdrawal of Drug	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 PL Sections 2 and 3 Warning regarding the potential for severe exacerbation of disease after ozanimod discontinuation and advice on monitoring and treatment is included in SmPC Section 4.4 and PL Sections 2 and 3. Advice to monitor patients for infections for up to 3 months after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	ORION study. Follow-up after discontinuation in Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

Table 11: Use in Patients Over 55 Years

Missing Information: Use in Patients Over 55 Years	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	ORION study. Long-term follow-up of Study RPC01-3001. See Section 1.5 of this summary for an overview of the postauthorisation development plan.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ozanimod.

1.5.2. Other Studies in Postauthorisation Development Plan

ORION Study - Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-Term Non-Interventional Study

Purpose of the study: The primary objective of this MS PASS is to evaluate the long-term safety profile of ozanimod in the real world setting.

Long-term Follow-up of Study RPC01-3001

Purpose of the study: To characterise the long-term safety of ozanimod in patients with relapsing MS.

1.6. References for RMP Summary

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