SUMMARY OF THE RISK MANAGEMENT PLAN FOR ZEPOSIA® (OZANIMOD)

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Disclaimer:

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® (OZANIMOD) 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® (OZANIMOD) in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of ZEPOSIA® (OZANIMOD).

SUMMARY OF THE RISK MANAGEMENT PLAN

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.

I. 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, and for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent (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 website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/zeposia.

II. 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.

II.A 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).

List of important risks and missing information

Important identified risks	Serious infection in patients with weakened immune systems (serious opportunistic infections including progressive multifocal leukoencephalopathy [PML])
	Swelling of a part of the retina (macular oedema)
	Severe liver injury
Important potential risks	Symptomatic slow heart rate (HR; symptomatic bradycardia)
	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)
	Blood clots (thromboembolic events)
	Risk of colorectal cancer (UC indication)
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

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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Serious Infections in Patients with Weakened Immune Systems (Serious Opportunistic Infections Including PML)	
Evidence for linking the risk to the medicine	A case of PML (a rare infection of the brain) has been observed with ozanimod treatment in the MS clinical trial RPC01-3001 open-label extension (OLE) study.
Risk factors and risk groups	Patients with prolonged and profound lymphopaenia (reduced white blood cells) 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. Package Leaflet (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 to discontinue ozanimod if PML is confirmed is included in SmPC Section 4.4. 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 magnetic resonance imaging findings that physicians should be vigilant for signs 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. Patients are advised not to take ozanimod if they have severe infection and to consult their doctor if they develop infections (PL Section 2). Patients are advised to consult their doctor or pharmacist before taking ozanimod if they notice symptoms that may be due to PML, in PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
Swelling of a part of the retina (macular oedema)	
Evidence for linking the risk to the medicine	An external review panel identified 3 cases of macular oedema with ozanimod 0.92 mg in the UC studies RPC01-202 and RPC01-3101 and 1 case of cystoid macular oedema with ozanimod 0.92 mg in the UC OLE study (Study RPC01-3102). All 4 cases of confirmed macular oedema were identified with optical coherence tomography findings consistent with macular oedema, and all cases

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	were associated with pre-existing risk factors or comorbid conditions that are known to cause macular oedema. No trend in central foveal thickness changes was noted over time. All 4 cases of macular oedema resolved. In the MS studies, for 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). Upon completion of the OLE study (RPC01-3001), two more confirmed cases of macular oedema were reported to a total of 5 cases. Following adjudication by a panel of ophthalmology experts including two neuro-ophthalmologists and a retinal specialist, 7 out of 9 cases were confounded by pre-existing risk factors including a history of macular oedema, uveitis, laser surgery, macular pucker, other ocular inflammation, or trauma. No clear time to onset pattern was identified. In 2 cases, drug was continued. In the remaining 7 cases, upon drug discontinuation, 6 cases showed full recovery and the case with trauma was stable. Post Marketing Experience As of 01-Apr-2023, since marketing approval 13 cases of macular oedema were reported from sources other than Company-sponsored clinical trials. At least in 4 cases, time to event onset was within 90 days from the start of ozanimod. In half of these cases there was a presence of known risk factors, such as uveitis, diabetes mellitus and cataract surgery. While most reports had limited information, in 3 cases the diagnosis by an ophthalmologist was reported. In one case, the patient with a history of hyperglycemia presented with blurry vision and was diagnosed with bilateral macular oedema after 7 months on ozanimod for UC.
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 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	Study RPC01-3102 (UC patients). Study IM047-1037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Severe Liver Injury	
Evidence for linking the risk to the medicine	Severe DILI is considered to be of public health concern. The majority of liver-related events in the ozanimod clinical studies (predominately ALT and GGT elevations) were mild to moderate in intensity and resolved while continuing treatment. Section 4.4 of the SmPC states that elevations of

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aminotransferases, gamma glutamyl transferase (GGT), and bilirubin have been reported in patients treated with ozanimod (see SmPC section 4.8). Signs of liver injury, including elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as 10 days after the first dose. Severe liver injury may result in the need for a liver transplant.

During the Induction Period for UC study RPC01-3101, elevations of ALT above 5-fold the ULN occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. Elevations of ALT above 3-fold the ULN occurred in 2.6% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. In the Study RPC01-3101 Maintenance Period, 0.9% of patients treated with ozanimod 0.92 mg and no patients who received placebo had elevations 5-fold the ULN or greater. Elevations of 3-fold the ULN occurred in 2.3% of patients treated with ozanimod 0.92 mg and none who received placebo.

In the UC studies (Pool G), elevations in ALT > 3 × ULN were observed in 6.0% of patients treated with ozanimod 0.92 mg and 0.2% of patients who received placebo. Of the ozanimod-treated patients, the majority (approximately 96% on ozanimod 0.92 mg) continued treatment with ozanimod, with values returning to ≤ 3 × ULN within approximately 2 weeks. The majority of ALT elevations were isolated cases, as evidenced by the low incidence of consecutive elevations > 3 × ULN (2.0% of patients treated with ozanimod 0.92 mg in Pool G) or > 5 × ULN (0.3% in Pool G). Similarly, the incidence of total bilirubin elevations > 2 × ULN was 1.1% in Pool G.

Two patients in Pool G had TEAEs reported by the Investigator as DILI. Both patients had mild (≥ 2 × ULN) nonserious, but persistent ALT elevations (after starting ozanimod treatment in OLE Study RPC013102), with ALT returning to near normal values (< 1.5 × ULN) with continued ozanimod treatment. The TEAEs were not associated with any symptoms or other laboratory changes and did not require any treatment. One patient was discontinued from Study RPC01-3102 due to persistent ALT elevation; the second patient continued in the OLE study.

Overall, in UC clinical studies, the discontinuation rate because of elevations in hepatic enzymes was 0.4% of patients with UC treated with ozanimod in both Induction and Maintenance Periods, and none in patients who received placebo in either period.

In active-controlled MS clinical trials, elevations of ALT to 5-fold the ULN or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on 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 AST were ≥ 3-fold the ULN together with bilirubin > 2fold the ULN in clinical trials, no cases of severe DILI (confirmed Hy's Law cases) were observed with ozanimod.

In the RPC01-3001, OLE study elevations of ALT > 3-fold the ULN occurred in 3.7% of patients, and elevations > 5-fold the ULN in 0.8% of patients treated

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	with ozanimod. About 25% of ALT elevations > 3-fold the ULN were within the first year, and about 50% of ALT elevations > 3-fold the ULN occurred after 24 months on the study. The incidence of ALT elevation > 3 fold the ULN on consecutive post-baseline assessment was 22 (0.9%), and ALT > 5 fold the ULN was 6 (0.2%). In the ozanimod clinical development program (Pool D), 14 patients experienced concurrent elevations of ALT or AST ≥ 3 × ULN and bilirubin > 2 × ULN. Review of unblinded cases (except those with clear alternative aetiology provided by Investigator) by an external panel of expert hepatologists concluded that there were no cases that met Hy's Law due to alternate explanations and the pattern of abnormalities. A spontaneous (post marketing) report of acute hepatic failure requiring liver transplantation was identified during routine surveillance activities in a patient treated with ozanimod for RRMS. A 50-year-old female patient with history of NASH and intermittent elevations of liver enzymes for about 10 years, experienced jaundice approximately 10 days after starting ozanimod, and continued taking medication for another 3 weeks. The patient was hospitalized with acute hepatic failure and successfully treated with liver transplant. The patient was also taking mirtazapine, levothyroxine, bisoprolol, and paracetamol at the time of event onset.
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). Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day in SmPC Sections 4.2 and 5.2. 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.
	Additional risk minimisation measures: – Healthcare Professional checklist – Patient/caregiver's guide
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.

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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. Two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported, both of which were detected by continuous cardiac monitoring overnight, and neither of which was associated with an adverse event (AE) or required treatment. In UC clinical studies Induction Period, which implemented dose escalation (Pool F), there was a modest (0.7 bpm) maximum mean reduction from baseline in HR during the first 6 hours post-dose on Day 1. This reduction was not associated with clinically significant bradycardia or conduction effects (eg, second-degree type 2 or third-degree atrioventricular block). No symptomatic bradycardia occurred during controlled studies. During hourly cardiac monitoring, one patient in an open-label cohort with a pre-dose HR of 56 bpm experienced headache, nausea and light-headedness after the first dose of ozanimod. The lowest reported HR was 43 bpm at Hour 2, which recovered to above baseline by Hour 5. No treatment or extended monitoring was required. As discussed above, two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported. One patient in Study RPC01-202, experienced HR ≤ 40 bpm. The patient's HR during the first 6 hours after dosing on Day 1 (approximately 9 am to 3 pm) was ≥ 64 bpm, and the patient experienced the minimal HR of 38 bpm at 2 am. Over 24-hour Holter monitoring, maximum HR was 133 bpm and mean HR was 80 bpm. This event was not associated with an AE and did not require treatment. 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 towards baseline at Hour 6. With the use of a dose 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 pre-treatment 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. One patient in Study RPC01-201A, had a HR of 39 bpm at Hour 20 post-dose on Day 8, which returned to normal (60 bpm) at Hours 23 and 24 the same day. This occurrence was not associated with an AE and did not require treatment. In the RPC01-3001, OLE study, two additional events of nonserious symptomatic bradycardia were reported in two patients. Both events resolved without intervention and 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.

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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	Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
Important Potential Risk: Cancer (Malignancy)	
Evidence for linking the risk to the medicine	Malignancies are identified by medical review of all TEAEs (preferred terms [PTs]) in the System Organ Class (SOC) Neoplasms benign, malignant and unspecified (incl. cysts and polyps) for the UC population. Events of colorectal carcinoma and high-grade dysplasia are also specifically monitored in the UC population. In total, 14 malignancies were observed in the UC studies: 6 NMSCs and 8 other malignancies. In UC studies (Pool G), malignancies were reported in 1.0% of patients in the ozanimod 0.92 mg treatment group and 0.4% in the placebo group. Both of the patients in the placebo group had received ozanimod during the Induction Period prior to being randomised to placebo maintenance. No malignancies were observed for patients exclusively exposed to placebo. Similar to MS, the overall incidence of malignancies with ozanimod is generally in line with rates reported in the literature in the UC population and the general population in the same age range. In the MS studies, for 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. In the RPC01-3001, OLE study, there were 29 treatment-emergent malignancies (excluding NMSCs) and 12 NMSCs. 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,

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	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 antineoplastic non-corticosteroid 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). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome)	
Evidence for linking the risk to the medicine	No cases of PRES were reported in UC clinical studies. In the OLE (RPC01-3001) study, no cases of PRES were reported. In controlled MS 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, 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

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	PRES despite only moderate acute elevation of their blood pressure. In patients with PRES associated renal disease treated with antihypertensive medications, neurological deficits resolved within 2 weeks. 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. PRES in the setting of autonomic dysfunction may also be a complication of Guillain-Barré syndrome.
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.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
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	As of 22-Mar-2023, a total of 78 events of potential exposure during pregnancy have been reported in patients treated with ozanimod across all indications, including 14 reported for female patients in ozanimod clinical trials for UC and 57 reported for female patients in ozanimod clinical trials for MS. The remaining 7 potential pregnancies in clinical trial participants occurred in 6 patients with Crohn's disease and 1 healthy volunteer. In addition, there have been 29 pregnancies in partners of male patients receiving ozanimod (30 outcomes due to twins). Of these, there have been 21 live births (13 normal; 5 premature, including 1 set of twins; and 3 with congenital abnormalities, including Hirschsprung's disease, congenital hydrocele, and partial atrioventricular septal defect), 1 ongoing pregnancy, 1 spontaneous early loss and 7 lost to follow-up. In partners of ozanimod-treated male participants in the ozanimod clinical development program, no drug related AEs (as assessed by Investigator and Sponsor) were reported. 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.

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	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). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide – Pregnancy specific patient reminder card
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients)
Blood Clots (Thromboembolic Events)	
Evidence for linking the risk to the medicine	In the ozanimod UC clinical development programme, the incidence rate (IR) per 1000 person-years for thromboembolic (TE) related events was 5.2 and 4.0 for ozanimod and placebo, respectively. The majority of the TE events occurred in older aged patients with documented risk factors. In MS controlled Phase 3 relapsing remitting MS studies (Pool A1), the incidence of TE events were similar in ozanimod and IFN β-1a groups, with events reported in 2 patients in the ozanimod 1 mg treatment group, 3 patients in the ozanimod 0.5 mg group and 4 patients with IFN β-1a. The majority of the TE events occurred in patients with documented risk factors. In the RPC01-3001, OLE study, 13 additional serious TE events were reported.
Risk factors and risk groups	Elderly age, prolonged hospitalisation/immobilisation, cancer, thyroid disease, oral contraceptive use, surgery, and pre-existing cardiovascular disease including prior DVT/ischaemia, phlebitis or cerebrovascular ischaemic attack, and hypertension are risk factors for TE events. The risk of thromboembolism is also increased with inflammatory bowel disease. Lifestyle factors, including smoking, physical inactivity and increased weight are also associated with increased risk of TE events.
Risk minimisation measures	**Routine risk minimisation measures:** Use of ozanimod is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure (SmPC Section 4.3). Blood pressure should be regularly monitored during treatment with ozanimod (SmPC Section 4.4). **Additional risk minimisation measures** None proposed.

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Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study, MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
Risk of colorectal cancer (UC indication)	
Evidence for linking the risk to the medicine	Colorectal cancer and events indicative of advanced colonic neoplasia (including colon adenomas and dysplasia) are identified by medical review of all TEAEs (PTs) in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) and the Gastrointestinal SOC, for the UC population. In Pool G, 3 cases of colorectal cancer (CRC) were reported in the RPC01-3101 Maintenance Period, including 2 patients in the ozanimod 1 mg treatment group and in 1 patient re-randomised to the placebo treatment group during the Maintenance Period. Overall, in Pool G, colon adenoma was reported in 5 patients (including 4 patients on ozanimod treatment and 1 patient re-randomised to placebo in the RPC01-3101 Maintenance Period). Colon dysplasia was reported in 1 patient on placebo.
Risk factors and risk groups	Patients with chronic inflammatory bowel conditions such as UC are at increased risk of CRC and advanced colonic neoplasia. Risk factors for CRC among UC patients include younger age at onset, extensive colitis, longer disease duration, concomitant primary sclerosing cholangitis, family history of CRC, and persisting inflammation of the colon. Patients with extensive colitis have a 3-fold increase in risk of CRC and a 5-fold increase for those with long-standing extensive colitis. Many cancers also develop as a result of a combination of genetics, environmental factors and lifestyle. General 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 other radiation, exposure to chemicals or hormone replacement).
Risk minimisation measures	**Routine risk communication:** 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 antineoplastic non-corticosteroid immunosuppressive therapy, is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) See Section II.C of this summary for an overview of the postauthorisation development plan.

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	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study, MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
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 after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) See Section II.C of this summary for an overview of the postauthorisation development plan.
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	Study RPC01-3102 (UC patients). Study IM047-1037 (UC PASS). Study IM047-009 (ORION study, MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C Post-authorisation development plan

II.C.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.

II.C.2 Other studies in post-authorisation development plan

Postauthorisation Safety Study in UC (Study IM0471037)

Purpose of the study: To evaluate the long-term real-world safety of ozanimod, and specifically to further characterise the safety concerns following treatment with ozanimod in UC.

Long-term Follow-up of Study RPC01-3102 in UC

Purpose of the study: To characterise the long-term safety of ozanimod in patients with moderately to severely active UC.

ORION Study - Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-Term Non-Interventional Study (Study IM047-009)

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.