**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Zeposia 0.23 mg hard capsules
Zeposia 0.46 mg hard capsules
Zeposia 0.92 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zeposia 0.23 mg hard capsules

Each hard capsule contains ozanimod hydrochloride equivalent to 0.23 mg ozanimod.

Zeposia 0.46 mg hard capsules

Each hard capsule contains ozanimod hydrochloride equivalent to 0.46 mg ozanimod.

Zeposia 0.92 mg hard capsules

Each hard capsule contains ozanimod hydrochloride equivalent to 0.92 mg ozanimod.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule.

Zeposia 0.23 mg hard capsules

Light grey opaque hard capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.23 mg” on the body.

Zeposia 0.46 mg hard capsules

Light grey opaque body and orange opaque cap hard capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.46 mg” on the body.

Zeposia 0.92 mg hard capsules

Orange opaque hard capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.92 mg” on the body.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Multiple sclerosis

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

Ulcerative colitis

Zeposia is indicated 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.

### 4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis (MS) or ulcerative colitis (UC).

Posology

The recommended dose is 0.92 mg ozanimod once daily.

The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is required and shown below in Table 1. Following the 7-day dose escalation, the once daily dose is 0.92 mg, starting on Day 8.

**Table 1: Dose escalation regimen**

| | |
|---|---|
| Days 1 – 4 | 0.23 mg once daily |
| Days 5 – 7 | 0.46 mg once daily |
| Days 8 and thereafter | 0.92 mg once daily |

*Re-initiation of therapy following treatment interruption*
The same dose escalation regimen described in Table 1 is recommended when treatment is interrupted for:

- 1 day or more during the first 14 days of treatment.
- more than 7 consecutive days between Day 15 and Day 28 of treatment.
- more than 14 consecutive days after Day 28 of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

*Special populations*

*Adults over 55 years old and elderly population*
There are limited data available on RRMS patients > 55 years of age and on UC patients ≥ 65 years of age. No dose adjustment is needed in patients over 55 years of age. Caution should be used in MS patients over 55 years and in UC patients over 65 years of age, given the limited data available and potential for an increased risk of adverse reactions in this population, especially with long-term treatment (see section 5.1 and 5.2).

*Renal impairment*
No dose adjustment is necessary for patients with renal impairment.

*Hepatic impairment*
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh class A and B).
Ozanimod was not evaluated in patients with severe hepatic impairment. Therefore, patients with severe hepatic impairment (Child-Pugh class C) must not be treated with ozanimod (see sections 4.3 and 5.2).

*Paediatric population*
The safety and efficacy of Zeposia in children and adolescents aged below 18 years have not yet been established. No data are available.

Method of administration

Oral use.
The capsules can be taken with or without food.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Immunodeficient state (see section 4.4).
- Patients who in the last 6 months experienced myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or New York Heart Association (NYHA) Class III/IV heart failure.
- Patients with history or presence of second-degree atrioventricular (AV) block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker.
- Severe active infections, active chronic infections such as hepatitis and tuberculosis (see section 4.4).
- Active malignancies.
- Severe hepatic impairment (Child-Pugh class C).
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

## 4.4 Special warnings and precautions for use

Bradyarrhythmia

*Initiation of treatment with ozanimod*
Prior to treatment initiation with ozanimod, an ECG in all patients should be obtained to determine whether any pre-existing cardiac abnormalities are present. In patients with certain pre-existing conditions, first-dose monitoring is recommended (see below).

Initiation of ozanimod may result in transient reductions in heart rate (HR) (see sections 4.8 and 5.1), and, therefore the initial dose escalation regimen to reach the maintenance dose (0.92 mg) on day 8 should be followed (see section 4.2).

After the initial dose of ozanimod 0.23 mg, the HR decrease started at Hour 4, with the greatest mean reduction at Hour 5, returning towards baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases. Heart rates below 40 beats per minute were not observed. If necessary, the decrease in HR induced by ozanimod can be reversed by parenteral doses of atropine or isoprenaline.

Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (e.g. diltiazem and verapamil) because of the potential for additive effects on lowering HR. Beta-blockers and calcium-channel blockers treatment can be initiated in patients receiving stable doses of ozanimod.

The co-administration of ozanimod in patients on a beta-blocker in combination with a calcium channel blocker has not been studied (see section 4.5).

*First dose monitoring in patients with certain pre-existing cardiac conditions*
Due to the risk of transient decreases in HR with the initiation of ozanimod, first-dose, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended in patients with resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section 4.3).

Patients should be monitored with hourly pulse and blood pressure measurement during this 6-hour period. An ECG prior to and at the end of this 6-hour period is recommended.
Additional monitoring is recommended in patients if at hour 6 post-dose:

- heart rate is less than 45 bpm
- heart rate is the lowest value post-dose, suggesting that the maximum decrease in HR may not have occurred yet
- there is evidence of a new onset second-degree or higher AV block at the 6-hour post-dose ECG
- QTc interval ≥500 msec

In these cases, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If medical treatment is required, monitoring should be continued overnight, and a 6-hour monitoring period should be repeated after the second dose of ozanimod.

*Cardiologist advice should be obtained before initiation of ozanimod in the following patients to decide if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy*

- history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia;
- pre-existing significant QT interval prolongation (QTc greater than 500 msec) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium-channel blockers that may potentiate bradycardia;
- Patients on class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products, which have been associated with cases of torsades de pointes in patients with bradycardia have not been studied with ozanimod.

Liver function

Elevations of aminotransferases may occur in patients receiving ozanimod (see section 4.8).
Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with ozanimod. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted. If liver transaminases above 5 times the ULN are confirmed, treatment with ozanimod should be interrupted and only re-commenced once liver transaminase values have normalised.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and ozanimod should be discontinued if significant liver injury is confirmed. Resumption of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction. Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod (see section 4.2).

Ozanimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3).

Immunosuppressive effects

Ozanimod has an immunosuppressive effect that predisposes patients to a risk of infection, including opportunistic infections, and may increase the risk of developing malignancies, including those of the skin. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis (see section 4.3).

Infections

Ozanimod causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible retention of lymphocytes in the lymphoid tissues. Ozanimod may, therefore, increase the susceptibility to infections (see section 4.8).

A recent (i.e., within 6 months or after discontinuation of prior MS or UC therapy) complete blood cell count (CBC) should be obtained, including lymphocyte count, before initiation of ozanimod.

Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/L, if confirmed, should lead to interruption of ozanimod therapy until the level reaches $> 0.5 \times 10^9$/L when re-initiation of ozanimod can be considered.

The initiation of ozanimod administration in patients with any active infection should be delayed until the infection is resolved.

Patients should be instructed to report promptly symptoms of infection to their physician. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. If a patient develops a serious infection, treatment interruption with ozanimod should be considered.

Because the elimination of ozanimod after discontinuation may take up to 3 months, monitoring for infections should be continued throughout this period.

Prior and concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies

In MS and UC clinical studies, patients who received ozanimod were not to receive concomitant antineoplastic, non-corticosteroid immunosuppressive (e.g. azathioprine and 6-mercaptopurine in UC), or immune-modulating therapies used for treatment of MS and UC. Concomitant use of ozanimod with any of these therapies would be expected to increase the risk of immunosuppression and should be avoided.

In UC clinical studies, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of ozanimod, however, long-term data on concomitant use of ozanimod and corticosteroids are still limited. When switching to ozanimod from immunosuppressive medicinal products, the half-life and mode of action must be considered to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation.
Ozanimod can generally be started immediately after discontinuation of interferon (IFN).

Progressive multifocal leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised and may lead to death or severe disability. PML has been reported in patients treated with S1P receptor modulators, including ozanimod, and other therapies for MS and UC. JCV infection resulting in PML has been associated with some risk factors (e.g., polytherapy with immunosuppressants, severely immunocompromised patients). Typical

symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ozanimod should be discontinued.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations in patients taking ozanimod. The use of live attenuated vaccines should be avoided during and for 3 months after treatment with ozanimod.

If live attenuated vaccine immunizations are required, these should be administered at least 1 month prior to initiation of ozanimod. Varicella Zoster Virus (VZV) vaccination of patients without documented immunity to VZV is recommended prior to initiating treatment with ozanimod.

Cutaneous neoplasms

Half of the neoplasms reported with ozanimod in the MS controlled Phase 3 studies consisted of non-melanoma skin malignancies, with basal cell carcinoma presenting as the most common skin neoplasm and reported with similar incidence rates in the combined ozanimod (0.2%, 3 patients) and IFN ß-1a (0.1 %, 1 patient) groups.

In patients treated with ozanimod in UC controlled clinical studies one patient (0.2%) had squamous cell carcinoma of the skin, in the induction period, and one patient (0.4%) had basal cell carcinoma, in the maintenance period. There were no cases in patients who received placebo.

Since there is a potential risk of malignant skin growths, patients treated with ozanimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Macular oedema

Macular oedema with or without visual symptoms was observed with ozanimod (see section 4.8) in patients with pre-existing risk factors or comorbid conditions.

Patients with a history of uveitis or diabetes mellitus or underlying/co existing retinal disease are at increased risk of macular oedema (see section 4.8). It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo an ophthalmological evaluation prior to treatment initiation with ozanimod and have follow up evaluations while receiving therapy.

Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. A decision on whether ozanimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

Posterior reversible encephalopathy syndrome (PRES)

PRES is a syndrome characterised by sudden onset of severe headache, confusion, seizures and visual loss. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. In MS controlled clinical trials with ozanimod, one case of PRES was reported in a

patient with Guillain-Barré syndrome. If PRES is suspected, treatment with ozanimod should be discontinued.

Blood pressure effects

In MS and UC controlled clinical studies, hypertension was more frequently reported in patients treated with ozanimod than in patients treated with IFN β-1a IM (MS) or placebo (UC) and in patients receiving concomitant ozanimod and SSRIs or SNRIs (see section 4.8). Blood pressure should be regularly monitored during treatment with ozanimod.

Respiratory effects

Ozanimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

Concomitant medicinal products

The coadministration with inhibitors of monoamine oxidase (MAO), or CYP2C8 inducer (rifampicin) with ozanimod is not recommended (see section 4.5).

Women of childbearing potential

Due to risk to the foetus, ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment, and for 3 months after treatment discontinuation (see sections 4.3 and 4.6 and the information contained in the Healthcare Professional checklist).

Return of MS disease activity (rebound) after ozanimod discontinuation

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping ozanimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon ozanimod discontinuation and appropriate treatment should be instituted as required.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effect of inhibitors of the breast cancer resistance protein (BCRP) on ozanimod

Coadministration of ozanimod with ciclosporin, a strong BCRP inhibitor, had no effect on the exposure of ozanimod and its major active metabolites (CC112273 and CC1084037).

Effect of inhibitors of CYP2C8 on ozanimod

The coadministration of gemfibrozil (a strong inhibitor of CYP2C8) 600 mg twice daily at steady state and a single dose of ozanimod 0.46 mg increased exposure (AUC) of the major active metabolites by approximately 47% to 69%. Caution should be exercised for concomitant use of ozanimod with strong CYP2C8 inhibitors (e.g. gemfibrozil, clopidogrel).

Effect of inducers of CYP2C8 on ozanimod

The coadministration of rifampicin (a strong inducer of CYP3A and P-gp, and a moderate inducer of CYP2C8) 600 mg once daily at steady state and a single dose of ozanimod 0.92 mg reduced exposure (AUC) of major active metabolites by approximately 60% via CYP2C8 induction which may result in reduced clinical response. The coadministration of CYP2C8 inducers (i.e. rifampicin) with ozanimod is not recommended (see section 4.4).

Effect of inhibitors of monoamine oxidase (MAO) on ozanimod

The potential for clinical interaction with MAO inhibitors has not been studied. However, the coadministration with MAO-B inhibitors may decrease exposure of the major active metabolites and may result in reduced clinical response. The coadministration of MAO inhibitors (e.g., selegiline, phenelzine) with ozanimod is not recommended (see section 4.4).

Effects of ozanimod on medicinal products that slow heart rate or atrioventricular conduction (e.g., beta-blockers or calcium channel blockers)

In healthy subjects, a single dose of ozanimod 0.23 mg with steady state propranolol long acting 80 mg once daily or diltiazem 240 mg once daily did not result in any additional clinically meaningful changes in HR and PR interval compared to either propranolol or diltiazem alone. Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (see section 4.4). Patients on other bradycardic medicinal products and on antiarrhythmic medicinal products (which have been associated with cases of torsades de pointes in patients with bradycardia) have not been studied with ozanimod.

Vaccination

During and for up to 3 months after treatment with ozanimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should, therefore, be avoided during and for up to 3 months after treatment with ozanimod (see section 4.4).

Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies

Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies should not be coadministered due to the risk of additive immune system effects (see sections 4.3 and 4.4).

Paediatric population

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

Zeposia is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the risk to the foetus. Women of childbearing potential must use effective contraception during ozanimod treatment and for 3 months after treatment discontinuation (see section 4.4).

Specific measures are also included in the Healthcare Professional checklist. These measures must be implemented before ozanimod is prescribed to female patients and during treatment.

When stopping ozanimod therapy for planning a pregnancy the possible return of disease activity should be considered (see section 4.4).

Pregnancy

There are no or limited amount of data from the use of ozanimod in pregnant women.
Studies in animals have shown reproductive toxicity including foetal loss and anomalies, notably malformations of blood vessels, generalised oedema (anasarca), and malpositioned testes and vertebrae (see section 5.3). Sphingosine 1-phosphate is known to be involved in vascular formation during embryogenesis (see section 5.3).

Consequently, Zeposia is contraindicated during pregnancy (see section 4.3). Zeposia should be stopped 3 months before planning a pregnancy (see section 4.4). If a woman becomes pregnant during treatment, Zeposia must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Breast-feeding

Ozanimod/metabolites are excreted in milk of treated animals during lactation (see section 5.3). Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed.

Fertility

No fertility data are available in humans. In animal studies, no adverse effects on fertility were observed (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Zeposia has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (>5%) in controlled periods of the adult MS and UC clinical studies are nasopharyngitis , alanine aminotransferase (ALT) increased , and gamma-glutamyl transferase (GGT) increased.

The most common adverse reactions leading to discontinuation were related to liver enzyme elevations (1.1%) in the MS clinical studies. Liver enzyme elevations leading to discontinuation occurred in 0.4% of patients, in UC controlled clinical studies.
The overall safety profile was similar for patients with multiple sclerosis and ulcerative colitis.

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with ozanimod are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

**Table 2: Summary of adverse reactions reported in MS and UC clinical studies**

| SOC | Frequency | Adverse reaction |
|---|---|---|
| **Infections and infestations** | Very common | Nasopharyngitis |
| | Common | Pharyngitis, respiratory tract infection viral, urinary tract infection*, herpes zoster, herpes simplex |
| | | |
| | Rare | Progressive multifocal leukoencephalopathy |
| **Blood and lymphatic system disorders** | Very common | Lymphopenia |
| **Immune system disorders** | Uncommon | Hypersensitivity (including rash and urticaria*) |
| **Nervous system disorders** | Common | Headache |
| **Eye disorders** | Uncommon | Macular oedema** |
| **Cardiac disorders** | Common | Bradycardia* |
| **Vascular disorders** | Common | Hypertension*†, orthostatic hypotension |
| **General disorders and administration site conditions** | Common | Peripheral oedema |
| **Investigations** | Common | Alanine aminotransferase increased, gamma-glutamyl transferase increased, blood bilirubin increased, pulmonary function test abnormal*** |

*At least one of these adverse reactions was reported as serious
† Includes hypertension, essential hypertension, and blood pressure increased (see section 4.4).
** for patients with pre-existing factors (see section 4.4)
***including pulmonary function test decreased, spirometry abnormal, forced vital capacity decreased, carbon monoxide diffusing capacity decreased, forced expiratory volume decreased

Description of selected adverse reactions

*Elevated hepatic enzymes*
In MS clinical studies, 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 IFN β-1a IM. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients on ozanimod and 3.1% of patients on IFN β-1a IM. 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 2-4 weeks. 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 MS patients on ozanimod 0.92 mg and 0.8% of patients on IFN beta-1a IM.

In UC clinical studies, during the induction period, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo, and in the maintenance period elevations occurred in 0.9% and no patients, respectively. In the induction period, elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of UC patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo, and in the maintenance period elevations occurred in 2.3% and no patients, respectively. In controlled and uncontrolled UC clinical studies, the majority (96%) of patients with ALT greater than 3-fold the ULN continued treatment with ozanimod with values returning to less than 3-fold the ULN within approximately 2 to 4 weeks.

Overall, the discontinuation rate due to elevations in hepatic enzymes was 0.4% of patients treated with ozanimod 0.92 mg, and none in patients who received placebo in the controlled UC clinical studies.

*Bradyarrhythmia*
After the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in sitting/ supine HR occurred at Hour 5 on day 1 (decrease of 1.2 bpm in MS clinical studies and 0.7 bpm in the UC clinical studies), returning towards baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases.

In MS clinical studies, bradycardia was reported in 0.5% of patients treated with ozanimod versus 0% of patients treated with IFN β-1a IM on the day of treatment initiation (Day 1). After Day 1, the incidence of bradycardia was 0.8% on ozanimod versus 0.7% on IFN β-1a IM. (see section 5.1). Patients who experienced bradycardia were generally asymptomatic. Heart rates below 40 beats per minute were not observed.

In MS clinical studies, first-degree atrioventricular block was reported in 0.6% (5/882) of patients treated with ozanimod versus 0.2% (2/885) treated with IFN β-1a IM. Of the cases reported with ozanimod, 0.2% were reported on Day 1 and 0.3% were reported after Day 1.

In UC clinical studies, during the induction period, bradycardia was reported on the day of treatment initiation (Day 1), in 0.2% of patients treated with ozanimod and none in patients treated with placebo. After Day 1 bradycardia was reported in 0.2% of patients treated with ozanimod. During the maintenance period, bradycardia was not reported

*Increased blood pressure*
In MS clinical studies, patients treated with ozanimod had an average increase of approximately 1-2 mm Hg in systolic pressure over IFN β-1a IM, and approximately 1 mm Hg in diastolic pressure over IFN β-1a IM. The increase in systolic pressure was first detected after approximately 3 months of treatment initiation and remained stable throughout treatment.
Hypertension-related events (hypertension, essential hypertension, and blood pressure increased) were reported as an adverse reaction in 4.5% of patients treated with ozanimod 0.92 mg and in 2.3% of patients treated with IFN β-1a IM.

In UC clinical studies, during the induction period, patients treated with ozanimod had an average increase of 1.4 mm Hg in systolic pressure over placebo (3.7 vs 2.3 mm Hg) and 1.7 mm Hg in diastolic pressure over placebo (2.3 vs 0.6 mm Hg). During the maintenance period, patients treated with ozanimod had an average increase of 3.6 mm Hg in systolic pressure over placebo (5.1 vs 1.5 mm Hg) and 1.4 mm Hg in diastolic pressure over placebo (2.2 vs 0.8 mm Hg).

Hypertension was reported as an adverse reaction in 1.2% of patients treated with ozanimod 0.92 mg and none in patients treated with placebo in the induction period. In the maintenance period, hypertension was reported in 2.2% of patients in each treatment arm. Hypertensive crisis was reported in two patients receiving ozanimod, who recovered without treatment interruption, and one patient receiving placebo.

*Blood lymphocyte count reduction*
In MS clinical studies, 3.3% of patients and in UC controlled clinical studies, 3% of patients experienced lymphocyte counts less than $0.2 \times 10^9$/L with values generally resolving to greater than $0.2 \times 10^9$/L while remaining on treatment with ozanimod.

*Infections*
In MS clinical studies, the overall rate of infections (35%) with ozanimod 0.92 mg was similar to IFN β-1a IM. The overall rate of serious infections was similar between ozanimod (1%) and IFN β-1a IM (0.8%) in MS clinical studies.

In UC clinical studies, during the induction period, the overall rate of infections and rate of serious infections in patients treated with ozanimod or placebo were similar (9.9% vs. 10.7% and 0.8% vs. 0.4%, respectively). During the maintenance period, the overall rate of infections in patients treated with ozanimod was higher than in patients treated with placebo (23% vs. 12%) and the rate of serious infections was similar (0.9% vs. 1.8%).

Ozanimod increased the risk of herpes infections, upper respiratory tract infections and urinary tract infections.

*Herpetic infections*
In MS clinical studies, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ozanimod 0.92 mg and in 0.2% of patients on IFN β-1a IM.

In UC clinical studies, herpes zoster was reported in 0.4% of patients who received ozanimod 0.92 mg and none in patients who received placebo in the induction period. In the maintenance period, herpes zoster was reported in 2.2% of patients who received ozanimod 0.92 mg and in 0.4% of patients who received placebo. None were serious or disseminated.

*Respiratory system*
Minor dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were observed with ozanimod treatment. At months 3 and 12 of treatment in MS clinical studies, median changes from baseline in FEV1 (FVC) in the ozanimod 0.92 mg group were - 0.07 L and - 0.1 L (- 0.05 L and – 0.065 L), respectively, with smaller changes from baseline in the IFN ß-1a group (FEV1: - 0.01 L and - 0.04 L, FVC: 0.00 L and -0.02 L).

Similar to MS clinical studies, small mean reductions in pulmonary function tests were observed with ozanimod relative to placebo (FEV1 and FVC) during UC clinical studies, in the induction period. There were no further reductions with longer term treatment with ozanimod in the maintenance period and these small changes in pulmonary function tests were reversible in patients re-randomised to placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

In patients with overdose of ozanimod, monitor for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of HR and blood pressure are required, and ECGs should be performed (see sections 4.4 and 5.1). The decrease in HR induced by ozanimod can be reversed by parenteral atropine or isoprenaline.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA38

Mechanism of action

Ozanimod is a potent sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity to sphingosine 1-phosphate receptors 1 and 5. Ozanimod has minimal or no activity on $S1P_2$, $S1P_3$, and $S1P_4$. *In vitro*, ozanimod and its major active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. The mechanism by which ozanimod exerts therapeutic effects in MS and UC is unknown, but may involve the reduction of lymphocyte migration into the central nervous system (CNS) and intestine.

The ozanimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Ozanimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites including two major metabolites (see section 5.2). In humans, approximately 94% of circulating total active substances exposure are represented by ozanimod (6%) and the two major metabolites CC112273 (73%), and CC1084037 (15%) (see section 5.2).

Pharmacodynamic effects

*Reduction of peripheral blood lymphocytes*
In active-controlled MS and placebo-controlled UC clinical studies, mean lymphocyte counts decreased to approximately 45% of baseline by 3 months (approximate mean blood lymphocyte count $0.8 \times 10^9$/L) and remained stable during treatment with ozanimod. After discontinuing ozanimod 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was approximately 30 days, with approximately 80% to 90% of patients recovering to normal within 3 months (see sections 4.4 and 4.8).

*Reduction in faecal calprotectin (FCP)*
In patients with UC, treatment with ozanimod resulted in a decrease in the inflammatory marker, faecal calprotectin (FCP) during the induction period, which was then maintained throughout the maintenance period.

*Heart rate and rhythm*
Ozanimod may cause a transient reduction in HR on initiation of dosing (see sections 4.4 and 4.8). This negative chronotropic effect is mechanistically related to the activation of G-protein-coupled inwardly rectifying potassium (GIRK) channels via $S1P_1$ receptor stimulation by ozanimod and its active metabolites leading to cellular hyperpolarisation and reduced excitability with a maximal effect on HR seen within 5 hours post dose. Due to its functional antagonism at $S1P_1$ receptors, a dose escalation schedule with ozanimod 0.23 mg followed by 0.46 mg, and 0.92 mg successively desensitises GIRK channels until the maintenance dose is reached. After the dose escalation period, with continued administration of ozanimod, HR returns to baseline.

*Potential to prolong the QT interval*
In a randomised, positive - and placebo-controlled thorough QT study using a 14-day dose-escalation regimen of 0.23 mg daily for 4 days, 0.46 mg daily for 3 days, 0.92 mg daily for 3 days, and 1.84 mg daily for 4 days in healthy subjects, no evidence of QTc prolongation was observed as demonstrated by the upper boundary of the 95% one-sided confidence interval (CI) that was below the 10 ms. Concentration-QTc analysis for ozanimod and the major active metabolites CC112273 and CC1084037, using data from another Phase 1 study showed the upper boundary of the 95% CI for model derived QTc (corrected for placebo and baseline) below 10 ms at maximum concentrations achieved with ozanimod doses ≥0.92 mg once daily.

Clinical efficacy and safety

*Multiple sclerosis*

Ozanimod was evaluated in two randomised, double-blind, double-dummy, parallel-group, active controlled clinical trials of similar design and endpoints, in patients with relapsing remitting MS (RRMS). Study 1 – SUNBEAM, was a 1-year study with patients continuing assigned treatment beyond month 12 until the last enrolled patient completed the study. Study 2 -RADIANCE was a 2-year study.

The dose of ozanimod was 0.92 mg and 0.46 mg given orally once daily, with a starting dose of 0.23 mg on days 1-4, followed by an escalation to 0.46 mg on days 5-7, and followed by the assigned dose on day 8 and thereafter. The dose of IFN β-1a, the active comparator, was 30 mcg given intramuscularly once weekly.

Both studies included patients with active disease as defined by having at least one relapse within the prior year, or one relapse within the prior two years with evidence of at least a gadolinium-enhancing (GdE) lesion in the prior year and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.0.

Neurological evaluations were performed at baseline, every 3 months, and at the time of a suspected relapse. MRIs were performed at baseline (Studies 1 and 2), 6 months (SUNBEAM), 1 year (Studies 1 and 2), and 2 years (RADIANCE).

The primary outcome of both SUNBEAM and RADIANCE was the annualised relapse rate (ARR) over the treatment period (minimum of 12 months) for SUNBEAM and 24 months for RADIANCE. The key secondary outcome measures included 1) the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months; 2) the number of MRI T1 GdE lesions at 12 and 24 months; and 3) the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS sustained for 12 weeks. Confirmed disability progression was prospectively evaluated in a pooled analysis of Studies 1 and 2.

In SUNBEAM, 1346 patients were randomised to receive ozanimod 0.92 mg (n = 447), ozanimod 0.46 mg (n= 451), or IFN β-1a IM (n = 448); 94% of ozanimod treated 0.92 mg, 94% of ozanimod treated 0.46 mg, and 92% of IFN β-1a IM treated patients completed the study. In RADIANCE, 1313 patients were randomised to receive ozanimod 0.92 mg (n = 433), ozanimod 0.46 mg (n = 439), or IFN β-1a IM (n = 441); 90% of ozanimod treated 0.92 mg, 85% of ozanimod treated 0.46 mg, and 85% of IFN β-1a IM treated patients completed the study. Patients enrolled across the 2 studies had a mean age of 35.5 years (range 18-55), 67% were female, mean time since MS symptom onset was 6.7 years. The median EDSS score at baseline was 2.5; approximately one-third of the patients had been treated with a disease-modifying therapy (DMT), predominately interferon or glatiramer acetate. At baseline, the mean number of relapses in the prior year was 1.3 and 45% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The results for SUNBEAM and RADIANCE are shown in Table 3. The efficacy has been demonstrated for ozanimod 0.92 mg with a dose effect observed for study endpoints shown in Table 3. Demonstration of efficacy for 0.46 mg was less robust since this dose did not show a significant effect for the primary endpoint in RADIANCE when considering the preferred negative binomial model strategy.

**Table 3: Key clinical and MRI endpoints in RMS patients from Study 1 - SUNBEAM and Study 2 - RADIANCE**

| **Endpoints** | **SUNBEAM (≥ 1 year)*** | | **RADIANCE (2 year)** | |
|---|---|---|---|---|
| | **Ozanimod 0.92 mg (n=447) %** | **IFN β-1a IM 30 mcg (n=448) %** | **Ozanimod 0.92 mg (n=433) %** | **IFN β-1a IM 30 mcg (n=441) %** |
| **Clinical endpoints** | | | | |
| Annualized relapse rate (Primary endpoint) | 0.181 | 0.350 | 0.172 | 0.276 |
| Relative reduction | 48% (p<0.0001) | | 38% (p<0.0001) | |
| Proportion relapse-free** | 78% (*p=0.0002*)[1] | 66% | 76% (*p=0.0012*)[1] | 64% |
| Proportion with 3-month confirmed disability Progression (CDP)†[2] Hazard ratio (95% CI) | 7.6% Ozanimod vs. 7.8% IFN β-1a IM 0.95 (0.679, 1.330) | | | |
| Proportion with 6-month CDP†[2#] Hazard ratio (95% CI) | 5.8% Ozanimod vs. 4.0% IFN β-1a IM 1.413 (0.922, 2.165) | | | |
| **MRI endpoints** | | | | |
| Mean number of new or enlarging T2 hyperintense lesions per MRI[3] | 1.465 | 2.836 | 1.835 | 3.183 |
| Relative reduction | 48% (p<0.0001) | | 42% (p<0.0001) | |
| Mean number of T1 Gd enhancing lesions[4] | 0.160 | 0.433 | 0.176 | 0.373 |
| Relative reduction | 63% (p<0.0001) | | 53% (p=0.0006) | |

* Mean duration was 13.6 months
** Nominal p-value for endpoints not included in the hierarchical testing and not adjusted for multiplicity
† Disability progression defined as 1-point increase in EDSS confirmed 3 months or 6 months later
# In a post hoc analysis of 6-month CDP which included data from the open-label extension (Study 3), the HR (95% CI) was found to be 1.040 (0.730, 1.482).)
[1] Log rank test
[2] Prospectively planned pooled analysis of Studies 1 and 2
[3] Over 12 months for Study 1 and over 24 months for Study 2
[4] At 12 months for Study 1 and at 24 months for Study 2

In SUNBEAM and RADIANCE, treatment with ozanimod 0.92 mg resulted in reductions in mean percent change from baseline in normalised brain volume compared to IFN beta-1a IM (-0.41% versus -0.61%, and -0.71% versus -0.94%, respectively, nominal p-value <0.0001 for both studies).

The studies enrolled DMT naive and previously treated patients with active disease, as defined by clinical or imaging features. Post-hoc analyses of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of ozanimod on clinical and imaging endpoints was consistent with the overall population.

*Long-term Data*Patients who completed the Phase 3 SUNBEAM and RADIANCE studies could enter an open label extension study (Study 3 - DAYBREAK). Of the 751 patients initially randomised to ozanimod 0.92 mg and treated for up to 3 years, the (adjusted) ARR was 0.124 after the 2nd year of treatment.

*Ulcerative colitis*
The efficacy and safety of ozanimod were evaluated in two multicentre, randomised, double-blind, placebo-controlled clinical studies [TRUENORTH-I (induction period) and TRUENORTH-M

(maintenance period)] in adult patients, aged less than 75 years, with moderately to severely active ulcerative colitis. TRUENORTH-I included patients who were randomised 2:1 to ozanimod 0.92 mg or placebo. The 10-week induction period (TRUENORTH-I) was followed by a 42-week, randomised, withdrawal maintenance period (TRUENORTH-M) for a total of 52 weeks of therapy. Ozanimod was administered as monotherapy (i.e., without concomitant use of biologics and non-corticosteroid immunosuppressants) for UC.

The study included patients with moderately to severely active ulcerative colitis defined at baseline (week 0) as a Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥ 2.

*TRUENORTH-I (induction study)*
In TRUENORTH-I, patients were randomised to either ozanimod 0.92 mg given, orally once daily (n=429) or placebo (n=216) beginning with a dose titration (see section 4.2). Patients received concomitant aminosalicylates (e.g., mesalazine 71%; sulfasalazine 13%) and/or oral corticosteroids (33%) at a stable dose prior to and during the induction period.

There were 30% of patients who had an inadequate response, loss of response or intolerant to TNF blockers. Of these patients with prior biologic therapy, 63% received at least two or more biologics including TNF blockers; 36% failed to ever respond to at least one TNF blocker; 65% lost response to a TNF blocker; 47% received an integrin receptor blocker (e.g., vedolizumab). There were 41% of patients who failed and/or were intolerant to immunomodulators. At baseline, patients had a median Mayo score of 9, with 65% of patients less than or equal to 9 and 35% having greater than 9.

The primary endpoint was clinical remission at week 10, and the key secondary endpoints at week 10 were clinical response, endoscopic improvement, and mucosal healing.

A significantly greater proportion of patients treated with ozanimod achieved clinical remission, clinical response, endoscopic improvement, and mucosal healing compared to placebo at week 10 as shown in Table 4.

**Table 4: Proportion of patients meeting efficacy endpoints in the induction period from TRUENORTH-I (at week 10)**

| | **Ozanimod 0.92 mg (N=429)** | | **Placebo (N=216)** | | **Treatment Difference %[a] (95% CI)** |
|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | |
| **Clinical remission[b]** | **79** | **18%** | **13** | **6%** | **12% (7.5, 17.2)[f]** |
| Without prior TNF blocker exposure | 66/299 | 22% | 10/151 | 7% | |
| Prior TNF blocker exposure | 13/130 | 10% | 3/65 | 5% | |
| **Clinical response[c]** | **205** | **48%** | **56** | **26%** | **22% (14.4, 29.3)[f]** |
| Without prior TNF blocker exposure | 157/299 | 53% | 44/151 | 29% | |
| Prior TNF blocker exposure | 48/130 | 37% | 12/65 | 19% | |
| **Endoscopic improvement[d]** | **117** | **27%** | **25** | **12%** | **16% (9.7, 21.7)[f]** |
| Without prior TNF blocker exposure | 97/299 | 32% | 18/151 | 12% | |
| Prior TNF blocker exposure | 20/130 | 15% | 7/65 | 11% | |
| **Mucosal healing[e]** | **54** | **13%** | **8** | **4%** | **9% (4.9, 12.9)[g]** |

| | Ozanimod 0.92 mg (N=429) | | Placebo (N=216) | | Treatment Difference %[a] (95% CI) |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Without prior TNF blocker exposure | 47/299 | 16% | 6/151 | 4% | |
| Prior TNF blocker exposure | 7/130 | 5% | 2/65 | 3% | |

CI = confidence interval; TNF = tumour necrosis factor.
[a] Treatment difference (adjusted for stratification factors of prior TNF blocker exposure and corticosteroid use at baseline).
[b] Clinical remission is defined as: RBS = 0, SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS), and endoscopy subscore ≤ 1 without friability.
[c] Clinical response is defined as a reduction from baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 or an absolute RBS of ≤ 1 point.
[d] Endoscopic improvement is defined as a Mayo endoscopic score ≤ 1 without friability.
[e] Mucosal healing defined as both Mayo endoscopic score ≤ 1 point without friability and histological remission (Geboes score < 2.0, indicating no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils, and no crypt destruction, erosions, ulcerations, or granulation tissue)
[f] p<0.0001.
[g] p<0.001.

*Rectal bleeding (RBS) and stool frequency (SFS) subscores*
Decreases in rectal bleeding and stool frequency subscores were observed as early as week 2 (i.e., 1 week after completing the required 7-day dose titration) in patients treated with ozanimod. A nominally significantly greater proportion of subjects achieved symptomatic remission, defined as RBS=0, SFS ≤1 and a decrease from baseline of ≥1, with ozanimod 0.92 mg than with placebo at Week 5 (27% vs 15%) and at Week 10 of the Induction Period (37.5% versus 18.5%).

Patients who had a decrease from baseline in SFS and/or RBS of at least 1 point but did not achieve clinical response or clinical remission at week 10 of TRUENORTH-I, had an increased rate of symptomatic remission after an additional 5 weeks of ozanimod treatment, 21% (26/126). The rate of symptomatic remission in these patients continued to increase through an additional 46 weeks of treatment, 50% (41/82).

*TRUENORTH-M (maintenance study)*
In order to be randomised to treatment in the maintenance study (TRUENORTH-M), patients had to have received ozanimod 0.92 mg and be in clinical response at week 10 of the induction period. Patients could have come from either TRUENORTH-I or from a group who received ozanimod 0.92 mg open-label. Patients were (re)-randomised in a double-blinded fashion (1:1) to receive either ozanimod 0.92 mg (n=230) or placebo (n=227) for 42 weeks. The total study duration was 52 weeks, including both the induction and maintenance periods. Efficacy assessments were at week 52. Concomitant aminosalicylates were required to remain stable through week 52. Patients on concomitant corticosteroids were to taper their dose upon entering the maintenance period.

At study entry, 35% of patients were in clinical remission, 29% of patients were on corticosteroids and 31% of patients who were previously treated with TNF blockers.

As shown in the Table 5, the primary endpoint was the proportion of patients in clinical remission at week 52. Key secondary endpoints at week 52 were the proportion of patients with clinical response, endoscopic improvement, maintenance of clinical remission at week 52 in the subset of patients in remission at week 10, corticosteroid-free clinical remission, mucosal healing and durable clinical remission.

**Table 5: Proportion of patients meeting efficacy endpoints in the maintenance period in TRUENORTH-M (at week 52)**

| | Ozanimod 0.92 mg (N=230) | | Placebo (N=227) | | Treatment difference %[a] (95% CI) |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Clinical remission[b]** | **85** | **37%** | **42** | **19%** | **19% (10.8, 26.4)[i]** |
| Without prior TNF blocker exposure | 63/154 | 41% | 35/158 | 22% | |
| Prior TNF blocker exposure | 22/76 | 29% | 7/69 | 10% | |
| **Clinical response[c]** | **138** | **60%** | **93** | **41%** | **19% (10.4, 28.0)[i]** |
| Without prior TNF blocker exposure | 96/154 | 62% | 76/158 | 48% | |
| Prior TNF blocker exposure | 42/76 | 55% | 17/69 | 25% | |
| **Endoscopic improvement[d]** | **105** | **46%** | **60** | **26%** | **19% (11.0, 27.7)[j]** |
| Without prior TNF blocker exposure | 77/154 | 50% | 48/158 | 30% | |
| Prior TNF blocker exposure | 28/76 | 37% | 12/69 | 17% | |
| **Maintenance of clinical remission at week 52 in the subset of patients in remission at week 10[e]** | **41/79** | **52%** | **22/75** | **29%** | **24% (9.1, 38.6)[k]** |
| Without prior TNF blocker exposure | 37/64 | 58% | 19/58 | 33% | |
| Prior TNF blocker exposure | 4/15 | 27% | 3/17 | 18% | |
| **Corticosteroid-free clinical remission[f]** | **73** | **32%** | **38** | **17%** | **15% (7.8, 22.6)[j]** |
| Without prior TNF blocker exposure | 55/154 | 36% | 31/158 | 20% | |
| Prior TNF blocker exposure | 18/76 | 24% | 7/69 | 10% | |
| **Mucosal healing[g]** | **68** | **30%** | **32** | **14%** | **16% (8.2, 22.9)[j]** |
| Without prior TNF blocker exposure | 51/154 | 33% | 28/158 | 18% | |
| Prior TNF blocker exposure | 17/76 | 22% | 4/69 | 6% | |
| **Durable clinical remission[h]** | **41** | **18%** | **22** | **10%** | **8% (2.8, 13.6)[l]** |
| Without prior TNF blocker exposure | 37/154 | 24% | 19/158 | 12% | |
| Prior TNF blocker exposure | 4/76 | 5% | 3/69 | 4% | |

CI = confidence interval; TNF = tumor necrosis factor.

[a] Treatment difference (adjusted for stratification factors of clinical remission and concomitant corticosteroid use at week 10).

[b] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the baseline SFS) and endoscopy subscore ≤ 1 point without friability.

[c] Clinical response is defined as: A reduction from baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[d] Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point without friability.

[e] Maintenance of remission defined as clinical remission at week 52 in the subset of patients in clinical remission at week 10.

[f] Corticosteroid-free remission is defined as clinical remission at week 52 while off corticosteroids for ≥ 12 weeks.

[g] Mucosal healing is defined as both Mayo endoscopic score ≤ 1 without friability and histological remission (Geboes score < 2.0, indicating no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils, and no crypt destruction, erosions, ulcerations, or granulation tissue)

[h] Durable clinical remission is defined as clinical remission at week 10 and at week 52 in all subjects who entered the maintenance period.

[i] p<0.0001.

[j] p<0.001.

[k] p=0.0025.

[l] p=0.0030

*Steroid free mucosal healing and steroid-free (2-component) symptomatic remission*

A significantly greater proportion of patients continuously treated with ozanimod 0.92 mg vs re-randomised to placebo achieved corticosteroid-free (at least 12 weeks) symptomatic remission (42.2% ozanimod versus 30.4% placebo) and corticosteroid-free (at least 12 weeks) endoscopic improvement (40.0% ozanimod versus 23.3% placebo) at week 52.

*Histologic remission at week 10 and 52*
Histologic remission (defined as Geboes index score < 2.0 points), was assessed at week 10 of TRUENORTH-I and at week 52 of TRUENORTH-M. At week 10, a significantly greater proportion of patients treated with ozanimod 0.92 mg achieved histologic remission (18%) compared to patients treated with placebo (7 %). At week 52, maintenance of this effect was observed with a significantly greater proportion of patients in histologic remission in patients treated with ozanimod 0.92 mg (34%) compared to patients treated with placebo (16%).

*Long-term data*
Patients who did not achieve clinical response at the end of the induction period, lost response in the maintenance period or completed the TRUENORTH study were eligible to enter an open label extension study (OLE) and received ozanimod 0.92 mg. Among patients who entered the OLE, clinical remission, clinical response, endoscopic improvement, and symptomatic remission were generally maintained through week 142. No new safety concerns were identified in this study extension in patients with ulcerative colitis (with a mean treatment duration of 22 months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ozanimod in one or more subsets of the paediatric population in MS and UC (see section 4.2).

## 5.2 Pharmacokinetic properties

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites, including two major active metabolites, CC112273 and CC1084037, with similar activity and selectivity for $S1P_1$ and $S1P_5$ to the parent. The maximum plasma concentration ($C_{max}$) and area under the curve (AUC) for ozanimod, CC112273, and CC1084037 increased proportionally over the dose range of ozanimod 0.46 mg to 0.92 mg (0.5 to 1 times the recommended dose). Following multiple dosing, approximately 94% of circulating total active substances are represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%). At a dose of 0.92 mg orally once daily in RRMS, the geometric mean [coefficient of variation (CV%)] $C_{max}$ and $AUC_{0-24h}$ at steady state were 231.6 pg/mL (37.2%) and 4223 pg*h/mL (37.7%), respectively, for ozanimod and 6378 pg/mL (48.4%) and 132861 pg*h/mL (45.6%), respectively, for CC112273. $C_{max}$ and $AUC_{0-24h}$ for CC1084037 are approximately 20% of that for CC112273. Factors affecting CC112273 are applicable for CC1084037 as they are interconverting metabolites. Population pharmacokinetic analysis indicated that there were no meaningful differences in these pharmacokinetic parameters in patients with relapsing MS or UC.

Absorption

The $T_{max}$ of ozanimod is approximately 6–8 hours. The $T_{max}$ of CC112273 is approximately 10 hours. Administration of ozanimod with a high-fat, high-calorie meal had no effect on ozanimod exposure ($C_{max}$ and AUC). Therefore, ozanimod may be taken without regard to meals.

Distribution

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) was 5590 L (27%), indicating extensive tissue distribution. Binding of ozanimod to human plasma proteins is approximately 98.2%. Binding of CC112273 and CC1084037 to human plasma proteins is approximately 99.8% and 99.3%, respectively.

Biotransformation

Ozanimod is widely metabolised by multiple biotransformation pathways including aldehyde dehydrogenase and alcohol dehydrogenase (ALDH/ADH), cytochrome P450 (CYP) isoforms 3A4

and 1A1, and gut microflora and no single enzyme system predominates the overall metabolism. Following repeated dosing, the AUCs of the two major active metabolites CC112273 and CC1084037 exceed the AUC of ozanimod by 13-fold and 2.5-fold, respectively. *In vitro* studies indicated that monoamine oxidase B (MAO-B) is responsible for the formation of CC112273 (via an intermediate minor active metabolite RP101075) while CYP2C8 and oxido-reductases are involved in the metabolism of CC112273. CC1084037 is formed directly from CC112273 and undergoes reversible metabolism to CC112273. The interconversion between these 2 active metabolites is mediated by carbonyl reductases (CBR), aldo-keto reductase (AKR) 1C1/1C2, and/or 3β- and 11β- hydroxysteroid dehydrogenase (HSD).

Elimination

The mean (CV%) apparent oral clearance for ozanimod was approximately 192 L/h (37%). The mean (CV%) plasma half-life ($t_{1/2}$) of ozanimod was approximately 21 hours (15%). Steady state for ozanimod was achieved within 7 days, with the estimated accumulation ratio following repeated oral administration of 0.92 mg once daily of approximately 2.
The model-based mean (CV%) effective half-life ($t_{1/2}$) of CC112273 was approximately 11 days (104%) in RMS patients, with mean (CV%) time to steady state of approximately 45 days (45%) and accumulation ratio of approximately 16 (101%) indicating the predominance of CC112273 over ozanimod. Plasma levels of CC112273 and its direct, interconverting metabolite CC1084037 declined in parallel in the terminal phase, yielding similar $t_{1/2}$ for both metabolites. Steady state attainment and accumulation ratio for CC1084037 are expected to be similar to CC112273.
Following a single oral 0.92 mg dose of [$^{14}$C]-ozanimod, approximately 26% and 37% of the radioactivity was recovered from urine and faeces, respectively, primarily composed of inactive metabolites. Ozanimod, CC112273, and CC1084037 concentrations in urine were negligible, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273, and CC1084037.

Pharmacokinetics in specific groups of patients

*Renal impairment*
In a dedicated renal impairment trial, following a single oral dose of 0.23 mg ozanimod, exposures ($AUC_{last}$) for ozanimod and CC112273 were approximately 27% higher and 23% lower, respectively, in patients with end stage renal disease (N=8) compared to patients with normal renal function (n = 8). Based on this trial, renal impairment had no clinically important effects on pharmacokinetics of ozanimod or CC112273. No dose adjustment is needed in patients with renal impairment.

*Hepatic impairment*
In a dedicated hepatic impairment trial, following a single oral dose of 0.23 mg ozanimod, exposures ($AUC_{last}$) for ozanimod and CC112273 were approximately 11% lower and 31% lower, respectively, in patients with mild hepatic impairment (Child-Pugh A; n = 8) when compared to patients with normal hepatic function (n = 7). Exposures ($AUC_{last}$) for ozanimod and CC112273 were approximately 27% higher and 33% lower, respectively, in patients with moderate hepatic impairment (Child-Pugh B; N=8) when compared to patients with normal hepatic function (n = 8). These differences were not considered clinically meaningful. The pharmacokinetics of ozanimod were not evaluated in patients with severe hepatic impairment. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Use in patients with severe hepatic impairment is contraindicated (Child-Pugh class C) (see section 4.3).

*Elderly*
Population pharmacokinetic analysis showed that steady state exposure (AUC) of CC112273 in patients over 65 years of age were approximately 3 - 4% greater than patients 45 – 65 years of age and 27% greater than adult patients under 45 years of age. There is not a meaningful difference in the pharmacokinetics in elderly patients.

Paediatric population

No data are available on administration of ozanimod to paediatric or adolescent patients (< 18 years of age).

## 5.3 Preclinical safety data

In repeated dose toxicology studies in mice (up to 4 weeks), rats (up to 26 weeks) and monkeys (up to 39 weeks), ozanimod markedly affected the lymphoid system (lymphopenia, lymphoid atrophy and reduced antibody response) and increased lung weights and the incidence of mononuclear alveolar infiltrates, which is consistent with its primary activity at $S1P_1$ receptors (see section 5.1). At the no observed adverse effect levels in chronic toxicity studies, systemic exposures to the disproportionate main active and persistent human metabolites CC112273 and CC1084037 (see section 5.2), and even to the total human active substances (ozanimod combined with the mentioned metabolites), were lower than those expected in patients at the maximum human dose of 0.92 mg ozanimod.

Genotoxicity and carcinogenicity

Ozanimod and its main active human metabolites did not reveal a genotoxic potential *in vitro* and *in vivo*.
Ozanimod was evaluated for carcinogenicity in the 6-month Tg.rasH2 mouse bioassay and the two-year rat bioassay. In the two-year rat bioassay, no treatment-related tumours were present at any ozanimod dose. However, metabolite exposure at the highest dose tested, was 62% of the human exposure for CC112273 and 18% of the human exposure for CC1084037 at the maximum clinical dose of 0.92 mg ozanimod.
In the 6-month Tg.rasH2 mouse study, hemangiosarcomas increased in a statistically-significant and dose-related manner. At the low dose (8 mg/kg/day), the hemangiosarcoma incidence was increased statistically significant in males and in both males and females at the mid and high dose levels (25 mg/kg/day and 80 mg/kg/day) compared to concurrent controls. In contrast to rats and humans, mouse $S1P_1$ receptor agonism results in sustained production of placental growth factor 2 (PLGF2) and subsequently, persistent vascular endothelial cell mitoses, potentially leading to species specific hemangiosarcomas with $S1P_1$ agonists. Therefore, $S1P_1$ receptor agonism related hemangiosarcomas in mice may be species specific and not predictive of a risk in humans.
No other treatment-related tumours were present at any dose in the Tg.rasH2 mouse study. At the lowest dose tested, exposure in Tg.rasH2 mice to the disproportionate two main active human metabolites was for CC112273 2.95 fold and for CC1084037 1.4 fold above the human exposure at the maximum clinical dose of 0.92 mg ozanimod.

Reproductive toxicity

Ozanimod had no effect on male and female fertility up to approximately 150-fold the systemic exposure to total active substances (combined ozanimod and the metabolites CC112273 and CC1084037) at the maximum human dose of 0.92 mg ozanimod.
Embryofoetal development was adversely affected by maternal treatment with ozanimod, with low (rats) or no (rabbits) safety margins based on comparison of systemic exposures to total active substances, resulting in embryolethality and teratogenicity (generalised oedema/anasarca and malpositioned testes in rats, malpositioned caudal vertebrae and malformations of the great vessels in rabbits). The vascular findings in rats and rabbits are consistent with the expected $S1P_1$ pharmacology.
Pre- and post-natal development was not affected by ozanimod administration up to the 5.6-fold the systemic exposure to total active substances at the maximum human dose of 0.92 mg ozanimod.
Ozanimod and metabolites were present in rat milk.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content

Microcrystalline cellulose
Colloidal anhydrous silica
Croscarmellose sodium
Magnesium stearate

Capsule shell

*Zeposia 0.23 mg and 0.46 mg*
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Black iron oxide (E172)
Red iron oxide (E172).

*Zeposia 0.92 mg*
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172).

Printing ink

Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Concentrated ammonia solution(E527)
Potassium hydroxide (E525)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C.

### 6.5 Nature and contents of container

Polyvinyl chloride (pVC)/ polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters.

Treatment initiation pack: Zeposia 0.23 mg and 0.46 mg

Pack size of 7 hard capsules (4 x 0.23 mg, 3 x 0.46 mg).

Maintenance pack: Zeposia 0.92 mg

Pack size of 28 or 98 hard capsules.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

Treatment initiation pack - Zeposia 0.23 mg/ 0.46 mg hard capsules

EU/1/20/1442/001 (Pack size of 7 hard capsules)

Maintenance pack - Zeposia 0.92 mg hard capsules

EU/1/20/1442/002 (Pack size of 28 hard capsules)
EU/1/20/1442/003 (Pack size of 98 hard capsules)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2020

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Zeposia in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State (MS) where Zeposia is marketed, all Healthcare Professionals who intend to prescribe Zeposia are provided with a Healthcare Professional Information Pack, containing the following:
- Information on where to find latest Summary of Product Characteristics (SmPC);
- Healthcare Professional checklist;

- Patient/Caregiver's guide;
- Pregnancy-specific patient reminder card.

**Healthcare Professional Checklist**

The Healthcare Professional checklist shall contain the following key messages:

- Dose escalation at treatment initiation
  - Start treatment with 0.23 mg once daily on Days 1-4, then increase the dose to 0.46 mg once daily on Days 5-7. Following the 7-day dose escalation, the once daily dose is 0.92 mg, starting on Day 8.

- Re-initiation of therapy following treatment interruption
  - The same dose escalation regimen described above is recommended when treatment is interrupted for:
    - 1 day or more during the first 14 days of treatment.
    - more than 7 consecutive days between Day 15 and Day 28 of treatment.
    - more than 14 consecutive days after Day 28 of treatment.
- If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

- Monitoring requirements at treatment initiation:
  *Before first dose*
  - Perform baseline electrocardiogram (ECG) prior to the first dose of Zeposia;
  - Consider recent (within last 6 months) liver function test results for transaminase and bilirubin levels;
  - Consider recent (within 6 months or after discontinuation of prior therapy) complete blood cell count results, including lymphocyte count;
  - Arrange ophthalmological assessment before starting Zeposia treatment in patients with diabetes mellitus, uveitis, or a history of retinal disease.
  - A negative pregnancy test result in women of childbearing potential must be confirmed prior to starting Zeposia treatment.

  *Until 6 hours after first dose for patients requiring first dose observation*
  - In patients with certain pre-existing cardiac conditions (resting heart rate <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure)
    - Monitor for 6 hours after the first dose of Zeposia for signs and symptoms of symptomatic bradycardia, with hourly pulse and blood pressure measurement
    - Perform an ECG prior to and at the end of the 6-hour monitoring period.
  - Extended monitoring may be required in the following situations if at hour 6 post-dose
    - heart rate is less than 45 bpm
    - heart rate is the lowest value post-dose, suggesting that the maximum decrease in heart rate may not have occurred yet
    - there is evidence of a new onset second-degree or higher AV block at the 6- hour post-dose ECG
    - QTc interval ≥500 msec
- When initiating Zeposia in patients with:
  - History of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia;
  - Pre-existing significant QT interval prolongation (QTc greater than 500 msec) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium-channel blockers that may potentiate bradycardia;
  - Current class Ia (eg, quinidine, disopyramide) or class III (eg, amiodarone, sotalol) antiarrhythmic medicinal products;

A cardiologist should be consulted before initiating Zeposia to determine if Zeposia can safely be initiated and to determine the most appropriate monitoring strategy.

- Caution should be taken when initiating Zeposia in patients taking medicines known to decrease heart rate.

- Zeposia is contraindicated in patients with:
  - Immunodeficient state predisposing to systemic opportunistic infections;
  - Severe active infections, active chronic infections such as hepatitis and tuberculosis;
  - Active malignancies;
  - Severe hepatic impairment (Child-Pugh class C);
  - Myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation or New York Heart Association (NYHA) Class III/IV heart failure in the last 6 months;
  - History or presence of second-degree AV block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker;
  - During pregnancy and in women of childbearing potential not using effective contraception;
  - Hypersensitivity to the active substance or to any of the excipients.

- Zeposia reduces peripheral blood lymphocyte counts. Complete blood cell count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored periodically during treatment with Zeposia Treatment should be interrupted if lymphocyte count is confirmed as $<0.2 \times 10^9$/l and the re-initiation of Zeposia can be considered if the level reaches $> 0.5 \times 10^9$/l.

- Zeposia has an immunosuppressive effect that predisposes patients to a risk of infection, including opportunistic infections, and may increase the risk of developing malignancies, including those of the skin. Patients should be carefully monitored, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered on a case-by-case basis.
  - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Interruption of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory, or non-corticosteroid immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.
  - Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended. Caution patients against exposure to sunlight without protection. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to 3 months after discontinuation of treatment with Zeposia.
  - Prompt diagnostic evaluation should be performed in patients with symptoms of infection while receiving, or within 3 months of stopping, treatment with Zeposia
  - Prescribers should be vigilant for clinical symptoms including unexpected neurological or psychiatric symptoms or MRI findings suggestive of PML. If PML is suspected a complete physical and neurological examination (including the possibility of performing an MRI) should be performed and treatment with Zeposia should be withheld until PML has been excluded. If PML is confirmed, treatment with Zeposia should be discontinued.
  - The use of live attenuated vaccines should be avoided during and for 3 months after discontinuation of treatment with Zeposia. Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of varicella or documentation of a full course of varicella vaccination. If negative, VZV vaccination is recommended at least 1 month prior to treatment initiation with Zeposia.

- Zeposia is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
    - A negative pregnancy test result must be confirmed prior to starting treatment in women of childbearing potential. It must be repeated at suitable intervals.
    - Women of childbearing potential should be informed before treatment initiation about the risks of Zeposia to the foetus, facilitated by the pregnancy-specific patient reminder card.
    - Women of childbearing potential must use effective contraception during Zeposia treatment and for at least 3 months after discontinuation of treatment with Zeposia.
    - Zeposia should be stopped 3 months before planning a pregnancy.
    - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, Zeposia must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Zeposia treatment and ultrasonography examinations should be performed.
    - Disease activity may possibly return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy.

- Liver function (transaminase and bilirubin levels) should be monitored at Months 1, 3, 6, 9 and 12 during Zeposia therapy and periodically thereafter.

- Blood pressure should be regularly monitored during treatment with Zeposia.

- Patient who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. Patients with diabetes mellitus, uveitis or a history of retinal disease should undergo an ophthalmological evaluation prior to treatment initiation with ozanimod and have follow up evaluations while receiving therapy.
- Prescribers should provide patients/caregivers with the patient/caregiver guide and with the pregnancy-specific patient reminder card

**Patient/Caregiver's Guide**

The patient/caregiver's guide shall contain the following key messages:

- What Zeposia is and how it works;
- What multiple sclerosis is;
- What ulcerative colitis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG prior to receiving the first dose of Zeposia.
- Zeposia should not be used if you have had a heart attack, angina, stroke or mini-stroke (transient ischaemic attack), or certain types of severe heart failure in the last 6 months or if you have certain types of irregular or abnormal heartbeats (arrhythmia) – your doctor will check your heart before starting treatment. Caution should be taken with concomitant use of medicines that slow your heart rate. Therefore, patients should tell any doctor they see that they are being treated with Zeposia.
- For patients with certain heart conditions, heart rate should be monitored for 6 or more hours after the first dose of Zeposia, including hourly pulse and blood pressure checks. An ECG before and after the 6 hours should also be performed for these patients.
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea, or palpitations) after the first dose of Zeposia;
- Patients should inform their prescriber in case of treatment interruption, as the initial dose escalation regimen may need to be repeated, depending on duration of interruption and time since initiation of Zeposia treatment;

- Patients should report any unexpected neurological and/or psychiatric symptoms/signs (such as sudden onset of severe headache, confusion, seizures, progressive weakness, clumsiness and vision changes) or accelerated neurological deterioration to their doctors;
- Patients are recommended to have varicella zoster (chickenpox) vaccination 1 month before starting Zeposia treatment, if the patient is not protected and wants to be protected against the virus;
- Signs and symptoms of infection, which should be immediately reported to the prescriber during and up to 3 months after discontinuation of treatment with Zeposia;
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to 3 months after discontinuation of treatment with Zeposia;
- Zeposia must not be used during pregnancy or in women of childbearing potential who are not using effective contraception. Women of childbearing potential should:
    - Be informed about serious risks to the foetus;
    - Have a negative pregnancy test before starting Zeposia. It must be repeated at suitable intervals;
    - Be informed about the requirement of using effective contraception during and for at least 3 months after discontinuation of treatment with Zeposia;
    - Be informed that disease activity may possibly return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy;
    - Report immediately to the prescriber any (intended or unintended) pregnancy during and up to 3 months after discontinuation of treatment with Zeposia. Ultrasonography examinations should be offered if needed;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at Months 1, 3, 6, 9 and 12 during Zeposia therapy, and should be performed periodically thereafter;
- Blood pressure should be regularly monitored during treatment with Zeposia;
- Zeposia may increase the risk of skin cancer. Patients should limit their exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).

**Pregnancy-specific Patient Reminder Card**

The pregnancy-specific patient reminder card (for women of childbearing potential) shall contain the following key messages:

- Zeposia is contraindicated during pregnancy and in women of childbearing potential not using effective contraception;
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the teratogenic risk of Zeposia and required actions to minimise this risk;
- Women of childbearing potential must use effective contraception while taking Zeposia and for 3 months after treatment discontinuation;
- A pregnancy test must be carried out and negative results verified by the prescriber before starting treatment. It must be repeated at suitable intervals;
- If a woman becomes pregnant while on treatment, ozanimod must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Zeposia treatment and ultrasonography examinations should be performed;
- Zeposia should be stopped 3 months before planning a pregnancy;
- Disease activity may possibility return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Initiation pack containing 1-week of treatment**

## 1. NAME OF THE MEDICINAL PRODUCT

Zeposia 0.23 mg hard capsules
Zeposia 0.46 mg hard capsules
ozanimod

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.23 mg hard capsule contains 0.23 mg of ozanimod (as hydrochloride).
Each 0.46 mg hard capsule contains 0.46 mg of ozanimod (as hydrochloride).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Treatment initiation pack
Each pack of 7 hard capsules for a 1-week treatment schedule contains:
4 hard capsules of 0.23 mg
3 hard capsules of 0.46 mg

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Week 1
Day 1 - Day 7
Refer to the wallet card for daily dose

QR code to be included
www.zeposia-eu-pil.com

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1442/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Zeposia 0.23 mg
Zeposia 0.46 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2 D bar code carrying the unique identifier included

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister for treatment initiation pack**

## 1. NAME OF THE MEDICINAL PRODUCT

Zeposia 0.23 mg hard capsules
Zeposia 0.46 mg hard capsules
ozanimod

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton**

## 1. NAME OF THE MEDICINAL PRODUCT

Zeposia 0.92 mg hard capsules
ozanimod

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.92 mg hard capsule contains 0.92 mg of ozanimod (as hydrochloride).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 hard capsules
98 hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

QR code to be included
www.zeposia-eu-pil.com

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1442/002 (Pack size of 28 hard capsules)
EU/1/20/1442/003 (Pack size of 98 hard capsules)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Zeposia 0.92 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2 D bar code carrying the unique identifier included

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Zeposia 0.92 mg hard capsules
ozanimod

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Zeposia 0.23 mg hard capsules**
**Zeposia 0.46 mg hard capsules**
**Zeposia 0.92 mg hard capsules**
ozanimod

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Zeposia is and what it is used for

Zeposia contains the active substance ozanimod that belongs to a group of medicines which can reduce the number of white blood cells (lymphocytes) circulating freely round the body.

Zeposia is indicated for the following diseases:
- Multiple sclerosis
- Ulcerative colitis

Multiple sclerosis
Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease.
- Multiple sclerosis (MS) is a disease in which the immune system (the body's defenses, including white blood cells) wrongly attack the protective coat around the nerves in the brain and spinal cord. This stops the nerves from working properly and may result in symptoms such as: numbness, difficulty in walking, and problems with vision and balance.
- In relapsing remitting multiple sclerosis, attacks on the nerve cells are followed by periods of recovery. The symptoms may disappear during the recovery periods, but some problems may remain.

Zeposia helps to protect against attacks on the nerves by stopping certain white blood cells reaching the brain and spine where they could cause inflammation and damage the nerves protective coating.

Ulcerative colitis

Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

- Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Zeposia to reduce the signs and symptoms of your disease.

Zeposia helps to reduce the inflammation in ulcerative colitis by stopping certain white blood cells from reaching the intestinal lining.

## 2. What you need to know before you take Zeposia

**Do not take Zeposia:**

- if you are allergic to ozanimod or any of the other ingredients of this medicine (listed in section 6)
- if your healthcare professional has told you that you have a severely weakened immune system
- if you have had a heart attack, angina, stroke or mini-stroke (Transient Ischemic Attack - TIA), or certain types of severe heart failure in the last 6 months
- if you have certain types of irregular or abnormal heartbeats (arrhythmia) – your doctor will check your heart before starting treatment
- if you have severe infection such as hepatitis or tuberculosis
- if you have cancer
- if you have severe liver problems
- if you are pregnant or a women of childbearing potential not using effective contraception.

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Zeposia if:

- you have a slow heart rate or you are taking or have recently taken medicines that slow your heart rate (such as beta blockers or calcium channel blockers);
- you have untreated severe breathing problems when you sleep (severe sleep apnoea);
- you have problems with your liver;
- you have an infection;
- you have low levels of a type of white blood cell - called lymphocytes;
- you have never had, or are not sure if you have had chickenpox;
- you have recently had or are planning to have a vaccination;
- you or others notice worsening of your MS symptoms as well as any new or unfamiliar symptoms. These may be due to a rare infection of the brain called progressive multifocal leukoencephalopathy (PML);
- you have ever had problems with your vision or other symptoms of build-up of fluid in the central area of the retina called the macula (a condition called macular oedema);
- you have inflammation of the eye (uveitis);
- you have diabetes (which can cause problems with your eyes);
- you have severe lung disease (pulmonary fibrosis or chronic obstructive pulmonary disease);

Before you start taking Zeposia, your doctor will check your heart using an electrocardiogram (ECG). If you have certain heart conditions your doctor will monitor you for at least the first 6 hours after your first dose.

As Zeposia can increase your blood pressure, your doctor may want to check your blood pressure regularly.

While you are taking Zeposia (and for up to 3 months after you stop taking it), you may get infections more easily. Any infection that you already have may get worse. Talk to your doctor if you develop an infection.

During treatment with Zeposia, if you develop disturbance of vision, progressive weakness, clumsiness, memory loss or confusion, or if you have MS and you think your disease is getting progressively worse, speak to your doctor straight away. These symptoms may be due to PML, a rare brain infection that may lead to severe disability or death.

During treatment with Zeposia, if you develop a severe headache, feel confused, or have seizures (fits) and loss of vision, speak to your doctor straight away. These symptoms may be due to a syndrome called posterior reversible encephalopathy syndrome (PRES).

As Zeposia may increase the risk of skin cancer, you should limit your exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).

Women of childbearing potential
If used during pregnancy, Zeposia can harm the unborn baby. Before you start treatment with Zeposia, your doctor will explain the risk to you and ask you to do a pregnancy test in order to ensure that you are not pregnant. Your doctor will give you a card which explains why you should not become pregnant while taking Zeposia. It also explains what you should do to avoid becoming pregnant while you are taking Zeposia. You must use effective contraception during treatment and for 3 months after stopping treatment (see section *"Pregnancy and breast-feeding"*).

If any of these apply to you, tell your doctor or pharmacist before taking Zeposia.

**Worsening of MS after stopping Zeposia treatment**
Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Zeposia (see "If you stop taking Zeposia" in section 3).

**Children and adolescents**
Do not give this medicine to children and adolescents aged under 18 years. This is because Zeposia has not been studied in children and adolescents.

**Other medicines and Zeposia**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Zeposia can affect the way some other medicines work. Also some other medicines can affect the way Zeposia works.

In particular, before taking Zeposia, tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines:

- medicines which suppress or modulate your immune system (e.g. ciclosporin)
- medicines used to treat MS, such as alemtuzumab, beta interferon, dimethyl fumarate, glatiramer acetate, mitoxantrone, natalizumab or teriflunomide
- medicines used to treat ulcerative colitis, such as azathioprine and 6-mercaptopurine
- gemfibrozil to reduce levels of fats or cholesterol in the blood
- clopidogrel, medicine used to prevent blood clots
- rifampicin, an antibiotic for treating tuberculosis and other serious infections
- medicines called monoamine oxidase inhibitors for treating depression (e.g. phenelzine) or Parkinson's disease (e.g. selegiline)
- medicines that slow your heart rate (such as beta-blockers or calcium channel blockers)

- certain type of vaccines. Live attenuated vaccines should be avoided during and for 3 months after treatment.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
Do not use Zeposia during pregnancy, if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception. If Zeposia is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk before you start treatment with Zeposia and will ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Zeposia and for at least 3 months after you stop taking it. Ask your doctor about reliable methods of contraception.
Your doctor will give you a card which explains why you should not become pregnant while taking Zeposia.

If you do become pregnant while taking Zeposia, tell your doctor straight away. Your doctor will decide to stop treatment (see *"If you stop taking Zeposia"* in section 3). Specialised pre-natal monitoring will be performed.

Breast-feeding
You should not breast-feed while you are taking Zeposia. Zeposia can pass into breast milk and there is a risk of serious side effects for the baby.

**Driving and using machines**
Zeposia has no or negligible influence on your ability to drive and use machines.

**Zeposia contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

## 3. How to take Zeposia

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**How much to take**
When you first start taking Zeposia, you need to take at a low dose and gradually build up, to reduce any effect in slowing your heart rate.
- You will be given a 'treatment initiation pack' to help you start treatment in this way. It contains:
  - 4 light-grey capsules, containing 0.23 mg ozanimod. You take one of these on days 1 to 4 of treatment.
  - 3 light-grey and orange capsules, containing 0.46 mg ozanimod. You take one of these on days 5, 6 and 7.
- On day 8 and thereafter, once you have completed the 'initiation pack', you will move on to a 'maintenance pack' with orange capsules each containing the recommended dose of 0.92 mg ozanimod. You will continue regular treatment with one 0.92 mg capsule daily.

**How to take Zeposia**
- Zeposia is for oral use.
- Swallow the capsule whole.

- You can take the capsule either with or without food.

**If you take more Zeposia than you should**
If you take more Zeposia than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack and this leaflet with you.

**If you forget to take Zeposia**
- If you forget a dose of Zeposia, take it as soon as you remember. However, if you forget the dose for the whole day skip the missed dose and take the next dose at your usual time.
- Do not take a double dose to make up for a forgotten dose.
- If you miss one or more doses during the first 14 days of starting Zeposia, talk to your doctor about how to re-start your treatment.

**If you stop taking Zeposia**
- Do not stop taking Zeposia without talking to your doctor first.
- Talk to your doctor about how to re-start your treatment if you have stopped taking Zeposia:
  - for 1 day or more during the first 14 days of treatment
  - for more than 7 consecutive days between day 15 and day 28 of treatment
  - for more than 14 consecutive days after day 28 of treatment.

You will need to start the 'treatment initiation pack' again.

Zeposia will stay in your body for up to 3 months after you stop taking it. Your white blood cell count (lymphocyte count) may also remain low during this time and the side effects described in this leaflet may still occur (see *"Possible side effects"* in section 4).

Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Zeposia.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**
Tell your doctor or pharmacist immediately if you notice any of the serious side effects listed below:

- **Common:** may affect up to 1 in 10 people
  - slow heart rate
  - urinary tract infection
  - increase in blood pressure
- **Uncommon:** may affect up to 1 in 100 people
  - allergic reaction – the signs may include a rash.
- **Rare:** may affect up to 1 in 1,000 people
  - brain infection called progressive multifocal leukoencephalopathy (PML) (see section 2)

**Other side effects**
Tell your doctor or pharmacist if you notice any of the following side effects:

- **Very common:** may affect more than 1 in 10 people

- infections of the nose or nostrils, nasal cavity, mouth, throat (pharynx), or voice box (larynx) caused by viruses
- low level of a type of white blood cell – called lymphocytes

- **Common:** may affect up to 1 in 10 people
  - inflammation of the throat (pharyngitis)
  - respiratory infection (sign of lungs infection)
  - herpes zoster (shingles)
  - herpes simplex or cold sores (oral herpes)
  - headache
  - drop in blood pressure
  - swelling especially of the ankles and feet, due to fluid retention (peripheral oedema)
  - increased liver enzyme levels in blood tests (a sign of liver problems) or yellow pigmentation of the skin, mucus membrane or eyes (jaundice)
  - lung abnormalities which can cause breathlessness
- **Uncommon:** may affect up to 1 in 100 people
  - blurred vision (macular oedema)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Zeposia

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Do not use this medicine if you notice any damage or signs of tampering with the pack.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Zeposia contains**
- The active substance is ozanimod.
  - *Zeposia 0.23 mg hard capsules*
    Each hard capsule contains 0.23 mg of ozanimod (as hydrochloride).
  - *Zeposia 0.46 mg hard capsules*
    Each hard capsule contains 0.46 mg of ozanimod (as hydrochloride).
  - *Zeposia 0.92 mg hard capsules*
    Each hard capsule contains 0.92 mg of ozanimod (as hydrochloride).
- The other ingredients are
  - *Capsule content:*
    Microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate.
  - *Capsule shell:*
    - Each 0.23 mg capsule contains gelatin, titanium dioxide (E171), yellow iron oxide (E172), black iron oxide (E172) and red iron oxide (E172).

        - Each 0.46 mg capsule contains gelatin, titanium dioxide (E171), yellow iron oxide (E172), black iron oxide (E172) and red iron oxide (E172).
        - Each 0.92 mg capsule contains gelatin, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).
    - *Printing ink:* iron oxide black (E172), Shellac (E904), propylene glycol (E1520), concentrated ammonia solution (E527), potassium hydroxide (E525)

**What Zeposia looks like and contents of the pack**

- The Zeposia 0.23 mg, 14.3 mm hard capsule has light grey opaque cap and body imprinted in black ink with "OZA" on the cap and "0.23 mg" on the body.
- The Zeposia 0.46 mg, 14.3 mm hard capsule has orange opaque cap and light grey opaque body imprinted in black ink with "OZA" on the cap and "0.46 mg" on the body.
- The Zeposia 0.92 mg, 14.3 mm hard capsule has orange opaque cap and body imprinted in black ink with "OZA" on the cap and "0.92 mg" on the body.

Pack sizes

- Treatment initiation pack is a wallet pack containing 7 hard capsules: 4 x 0.23 mg hard capsules and 3 x 0.46 mg hard capsules.
- Maintenance pack containing 28 x 0.92 mg hard capsules or 98 x 0.92 mg hard capsules.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

**Manufacturer**
Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

**This leaflet was last revised in**

**Other sources of information**

Detailed and updated information on this medicine is available by scanning the QR code on the outer packaging with a smartphone. The same information is also available on the following URL : www.zeposia-eu-pil.com.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.