דצמבר 2021

Zeposia 0.23 mg, 0.46 mg, 0.92 mg, Capsules
זפוסיה 0.23 מ"ג, 0.46 מ"ג, 0.92 מ"ג, כמוסות

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) שמחה להודיע על רישום התוויה חדשה, Ulcerative Colitis (UC) לתכשירים שבנדון.

התוויות התכשיר כפי שאושרו ע"י משרד הבריאות הן:

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 moderately to severely active ulcerative colitis (UC) in adults.

המרכיב הפעיל: Ozanimod 0.23mg, 0.46mg or 0.92mg per capsules

העלונים לרופא ולצרכן עודכנו בהתאם. בנוסף עודכנו העלונים עם מידע בטיחותי חדש.

להלן העדכונים המהותיים בעלונים (ללא פירוט שינויים עריכתיים).

תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו אמצעי~~, החמרה מודגשת בצהוב.

למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו על ידי משרד הבריאות.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפס על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ.

בברכה,
יפעת זלינגר בן דוד
רוקחת ממונה
בריסטול-מאיירס סקוויב (ישראל)

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 moderately to severely active ulcerative colitis (UC) in adults.

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).
[…]

Special populations

Adults over 55 years old and elderly population
~~There are limited data available on RRMS patients > 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 0.92 mg ozanimod daily after they become 55 and older (see sections 5.1 and 5.2). No dose adjustment is needed in patients over 55 years of age.~~ 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 ~~> 55~~ 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).
[…]

4.4 Special warnings and precautions for use
[…]

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 ~~multiple sclerosis (~~MS~~)~~ and UC~~therapies.~~ JCV infection resulting in PML ~~has been observed in patients treated with MS therapies and~~ 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.
[…]

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.
[…]

Concomitant medicinal products

The coadministration with ~~inhibitors of the breast cancer resistance protein (BCRP),~~ inhibitors of monoamine oxidase (MAO), or CYP2C8 inducer (~~rifampin~~rifampicin) with ozanimod is not recommended (see section 4.5).
[…]

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).~~An inhibitor of the BCRP (ciclosporin) doubled the exposure (AUC) of the minor active metabolites which may subsequently lead to a similar increase in the major active metabolites and increase the risk of adverse reactions. The coadministration of BCRP inhibitors (e.g. ciclosporin and eltrombopag) with ozanimod is not recommended (see section 4.4).~~

[…]

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 ~~(11%)~~, alanine aminotransferase (ALT) increased ~~(5%)~~, and gamma-glutamyl transferase (GGT) increased ~~(5%)~~.

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 1: Summary of adverse reactions reported in MS and UC clinical studies

~~System Organ Class~~OC	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis
	Common	Pharyngitis, r~~R~~espiratory tract infection viral, u~~U~~rinary tract infection*, h~~H~~erpes zoster, ~~H~~ herpes simplex
	~~Uncommon~~	~~Herpes zoster~~
	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*†, o~~O~~rthostatic hypotension
General disorders and administration site conditions	Common	Peripheral oedema
Investigations	Common	Alanine aminotransferase increased, g~~G~~amma-glutamyl transferase increased, b~~B~~lood bilirubin increased, p~~P~~ulmonary 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. ~~In MS clinical studies, o~~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
~~In MS clinical studies, a~~After the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in sitting/ supine HR ~~of 1.2 bpm~~ 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 ~~to near~~towards baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases.
[…]

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 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 x 10^9/L with values generally resolving to greater than 0.2 x 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. ~~Ozanimod increased the risk of upper respiratory tract infections and urinary tract infection.~~ 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~~*Herpes zoster*~~
In MS clinical studies, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ~~Zeposia~~ 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 ~~1~~ 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.
[…]

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 ~~selectively~~ to sphingosine 1-phosphate receptors ~~subtypes~~ 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 $S1P_5$. ~~Ozanimod causes lymphocyte retention in lymphoid tissues.~~ 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 10-fold more selective for $S1P_1$ relative to $S1P_5$ and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$).~~ Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites including two major metabolites (see section 5.2). ~~*In vitro,*~~

~~ozanimod and its active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$.~~
In humans, approximately 94% of circulating total active ~~drug~~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
~~Ozanimod induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues.~~
In active-controlled MS and placebo-controlled UC clinical studies, mean lymphocyte counts decreased to approximately 45% of baseline ~~at~~ by 3 months (approximate mean blood lymphocyte count 0.8 x 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.
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Clinical efficacy and safety

Multiple sclerosis
[…]

Table 2: 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 ~~E~~endpoints				
Annualized ~~R~~relapse ~~R~~rate	0.181	0.350	0.172	0.276
(Primary ~~E~~endpoint) Relative ~~R~~reduction	48% (p<0.0001)		38% (p<0.0001)	
Proportion ~~R~~relapse-free**	78% (*p=0.0002*)[1]	66%	76% (*p=0.0012*)[1]	64%
Proportion with 3-month ~~C~~confirmed ~~D~~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 ~~R~~ratio (95% CI)	5.8% Ozanimod vs. 4.0% IFN β-1a IM 1.413 (0.922, 2.165)			

MRI ~~E~~endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI[3]	1.465	2.836	1.835	3.183
Relative ~~R~~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 ~~R~~reduction	63% (p<0.0001)		53% (p=0.0006)	

[…]

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]**
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%	

	Ozanimod 0.92 mg (N=230)		Placebo (N=227)		Treatment difference %[a] (95% CI)
	n	%	n	%	
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).

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 ~~drug exposure~~substances are ~~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.

[…]

Elderly

~~No pharmacokinetic data are available on administration of ozanimod to patients aged 55 years and over.~~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.

[…]

עדכונים מהותיים בעלון לצרכן

1. **למה מיועדת התרופה?**

- זפוסיה מותווית לטיפול במטופלים מבוגרים עם טרשת נפוצה התקפית-הפוגתית עם מחלה פעילה כפי שהוגדרה על ידי מאפיינים קליניים או באמצעות הדמיה.
- זפוסיה מותווית לטיפול במבוגרים עם קוליטיס כיבית (דלקת כיבית של המעי הגס) פעילה, בינונית עד חמורה.

[...]

קוליטיס כיבית (ulcerative colitis)

- קוליטיס כיבית היא מחלה דלקתית של המעי.

זפוסיה מסייעת בהפחתת הדלקת בקוליטיס כיבית על ידי עצירת תאי דם לבנים מסוימים מלהגיע לרירית המעי.

2. לפני השימוש בתרופה

[...]

במהלך הטיפול בזפוסיה, אם אתה מפתח הפרעה בראייה, חולשה מתגברת, התנהגות מגושמת, אובדן זיכרון או בלבול, או אם יש לך טרשת נפוצה ואתה חושב שהמחלה שלך מתקדמת ומחמירה, פנה מיד לרופא שלך. תסמינים אלו עשויים לנבוע מלויקואנצפלופתיה רב-מוקדית מתקדמת (PML), זיהום מוחי נדיר שעלול להוביל לנכות חמורה או למוות.

[...]

אינטראקציות/תגובות בין תרופתיות:

[...]

במיוחד, לפני שתיקח זפוסיה, ספר לרופא או לרוקח אם אתה לוקח או לקחת לאחרונה אחת מהתרופות הבאות:

- תרופות שמדכאות או מווסתות את מערכת החיסון (למשל ציקלוספורין ו~~אלטרומבופאג~~),
- ~~כולל~~ תרופות ~~אחרות~~ המשמשות לטיפול בטרשת נפוצה, כמו אלמטוזומאב, בטא אינטרפרון, דימתיל פומראט, גלטירמר אצטט, מיטוקסנטרון, נטליזומאב או טריפלונומיד
- תרופות המשמשות לטיפול בקוליטיס כיבית, כמו אזאתיופרין ו – 6-מרקפטופורין

[...]

מידע חשוב על חלק מהמרכיבים של התרופה

תכולת נתרן

תרופה זאת מכילה פחות מ – 1 מילימול (23 מ"ג) נתרן למנה, ונחשבת "נטולת נתרן".

[...]

4. תופעות לוואי

[...]

תופעות לוואי רציניות

[...]

- **תופעות לוואי נדירות (rare) תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000:**
  - זיהום במוח הנקרא לויקואנצפלופתיה רב-מוקדית מתקדמת (PML) (ראה פרק 2)

תופעות לוואי אחרות

[...]

- **תופעות לוואי שכיחות (common) תופעות שמופיעות ב – 1-10 משתמשים מתוך 100**:
  - דלקת של הגרון (דלקת הלוע (פרינגיטיס))
  - זיהום נשימתי (סימן של זיהום ריאות)
  - הרפס זוסטר (שלבקת חוגרת)
  - הרפס סימפלקס או פצעי קור (הרפס של הפה)
  - כאב ראש
  - נפילה בלחץ דם
  - נפיחות בעיקר של הקרסוליים וכפות הרגליים, עקב אצירת נוזלים (בצקת היקפית)
  - עלייה ברמות של אנזימי כבד בבדיקות דם (סימן של בעיות בכבד) או פיגמנטציה צהובה של העור, רקמות ריריות או העיניים (צהבת)
  - הפרעות בריאות שיכולות לגרום לקוצר נשימה
- **תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000**:
  - ~~הרפס זוסטר (שלבת חוגרת)~~
  - ראייה מטושטשת (בצקת מקולרית)

[...]