Bristol Myers Squibb™

Oregon Health Authority

July 23, 2020

Dear Oregon Health Authority,

Thank you for your request about Zeposia® (ozanimod) which has been forwarded to Medical Information by Wendy Bibeau. You have requested information regarding Zeposia (ozanimod) written testimony for Oregon Pharmaceutical and Therapeutics Drug Utilization Review.

Please note that Bristol-Myers Squibb does not recommend the use of ZEPOSIA in any manner inconsistent with that described in the Full Prescribing Information. Please review the end of this letter for full indications and boxed warnings, and consult the attached Full Prescribing Information for ZEPOSIA. For information concerning ongoing clinical trials, please visit www.ClinicalTrials.gov.

Zeposia® - Oregon Health Authority Cover Letter

Summary

Thank you for your unsolicited request for a written testimony for Zeposia® (ozanimod) to review at the Oregon Health Authority P&T meeting on August 6th.

As requested, please find the following attached:

–Zeposia® Oregon Health Authority Written Testimony

Important Safety Information

Contraindications:

- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA
- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued
- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects
- Use of live *attenuated* vaccines should be avoided during and for 3 months after treatment with ZEPOSIA.

If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated

Macular edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended

Severe Increase in Disability After Stopping ZEPOSIA: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment so patients should be monitored upon discontinuation

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA

Most common Adverse Reactions (≥ 4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

For additional safety information, please see the full Prescribing Information and Medication Guide

Product Indication: Zeposia® (ozanimod):
ZEPOSIA®(ozanimod) is indicated for the following uses:

- For the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please refer to the end of this information packet for the following:

- Reporting adverse event cases or product quality complaints, or to provide information on exposure to a BMS product during pregnancy or lactation.

With the aim to continuously improve the quality of our service we would like to request you complete a brief satisfaction survey. It will only take you 3 minutes to complete. The survey can be accessed at the below link:
Click here

We trust that you will find this information helpful. If you have further questions or require additional information, please contact BMS Medical Information Department at 1-800-321-1335.

Sincerely,
BMS Medical Information

For Your Consideration:

Adverse Event / Pregnancy

If you become aware of a patient who has experienced an adverse event with a BMS product, has received treatment with a BMS product during pregnancy or lactation, or has become pregnant while her partner received treatment with a BMS product, please contact us at 1-800-721-5072.

Bristol Myers Squibb™

Note: The purpose of this document is to provide the clinical and/or pharmacoeconomic information regarding ZEPOSIA® (ozanimod) as requested; it is not intended to be used for any other purpose. This document contains relevant information for ZEPOSIA, which may or may not be included in the U.S. Prescribing Information (USPI). BMS does not suggest or recommend the use of ZEPOSIA in any manner other than as described in the USPI.

ZEPOSIA® (ozanimod) capsules, for oral use

Indications: Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, & active secondary progressive disease, in adults.[1]

Recommended Dosage and Administration:

Assessments Prior to First Dose of ZEPOSIA: Before initiation of treatment with ZEPOSIA, assess the following:

Complete Blood Count: Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count, including lymphocyte count.

Cardiac Evaluation: Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought.

Liver Function Tests: Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels.

Ophthalmic Assessment: In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula.

Current or Prior Medications:

- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA.
- Determine if patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction.

Vaccinations: Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA. If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

Dosing Information:

Maintenance Dosage: After initial titration, the recommended maintenance dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8. ZEPOSIA capsules should be swallowed whole and can be administered with or without food.

Treatment Initiation: Initiate ZEPOSIA with a 7-day titration, as shown in Table.

Dose Titration Regimen

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

Re-initiation of ZEPOSIA After Treatment Interruption: If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

How Supplied: Capsules: 0.23 mg, 0.46 mg, 0.92 mg (3)

Mechanism of Action: Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ozanimod exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

Registrational Phase 3 Studies

SUNBEAM, a Phase 3, multicenter, randomized, double-blind, double-dummy study, compared the efficacy & safety of once-daily oral ozanimod 0.92 mg (n= 447), ozanimod 0.46 mg (n=451), & weekly intramuscular (IM) injection of interferon (IFN) β-1a 30 µg (n=448) in relapsing MS (RMS) adult pts.[2]

- Annualized relapse rate (ARR), primary endpoint, was 0.24 (95% CI, 0.19-0.31) for ozanimod 0.46 mg (31% reduction, *P*=.0013) & 0.18 (95% CI, 0.14-0.24) for ozanimod 0.92 mg (48% reduction, *P*<.0001) vs. 0.35 (95% CI, 0.28-0.44) for IFN β-1a 30 µg. Dose-dependent effects of ozanimod on ARR vs. IFN β-1a were consistent with the overall primary endpoint across pre-specified subgroups: baseline EDSS subgroups, disease-modifying therapy (DMT), history (naïve vs. experienced), GdE lesions (presence vs. absence), sex, & age.
- Both ozanimod 0.46 mg (25% relative reduction, *P*=.0032) & 0.92 mg (48% relative reduction, *P*<.0001) demonstrated a significant reduction in the number of new or enlarging T2 brain lesions over 12 months compared with the IFN β-1a 30 µg group.
- A significant reduction in the number of GdE brain lesions at 12 months was observed with both ozanimod 0.46 mg (34% relative reduction, *P*=.0182) & 0.92 mg (63% relative reduction, *P*<.0001) compared with IFN β-1a 30 µg.
- In a pre-specified pooled analysis of RADIANCE & SUNBEAM, no statistically significant difference was observed between ozanimod groups vs IFNβ-1a in time to 3-month confirmed disability progression (key secondary endpoint)

Safety

- Incidence of TEAEs was higher for IFN β-1a (n=336; 75.5%) than ozanimod 0.92 mg (n=268; 59.8%) or 0.46 mg (n=259; 57.2%). AE Discontinuation rates were 2.9% for ozanimod 0.92 mg; 1.6%, ozanimod 0.46 mg, & 3.6 % IFN β-1a.
- Incidence of serious TEAEs was similar across treatment groups & occurred in 13 (2.9%), 16 (3.5%) & 11 (2.5%) pts in the ozanimod 0.92 mg, 0.46 mg, & IFN β-1a group. No deaths occurred in the study
- *AEs identified as 'of special interest' in the study, cardiac abnormalities, serious or opportunistic infections, hepatotoxicity, ophthalmic abnormalities, pulmonary abnormalities, depression & malignancies, are summarized below.*
  - *Cardiac:* In first 6h after-ozanimod 0.23 mg initiation, greatest decline in mean supine HR was 1.8 bpm at 5h & no HR < 45 bpm observed; 1 case of symptomatic [headache; unconfirmed by HR (≥ 71 bpm)] that did not require treatment discontinuation, & 1 of asymptomatic bradycardia (serious TEAE that resolved) were reported,. No 2nd/3rd degree AV block TEAEs reported during study.
  - *Infections:* Percentages of pts with any infection ranged from 26.7%-28.9%, with herpes infection rates being 0.9% (n=4) for ozanimod 0.92mg; 0.7% (n=3), ozanimod 0.46 mg; & 1.1% (n=5), IFN-β-1a. No serious opportunistic infections occurred in ozanimod groups.
  - *ALC:* Mean ALC (all x 10^9 cells/L) declined at Month 3 in both ozanimod groups, but stabilized thereafter through Month 12. In the ozanimod 0.92 mg, ozanimod 0.42 mg & IFN-β-1a groups, mean ALC (% of baseline ALC) at Month 12 was 0.759 (42.8%), 0.963 (54.1%) & 1.764 (97.7%), respectively; mean minimum ALC during the study was 0.557, 0.755, & 1.324, respectively. 11 pts (ozanimod 0.92 mg) had an ALC < 0.2, but no associated opportunistic/serious infections.
  - *Hepatic:* ALT rose ≥ 3 x ULN in 19 (4.3%), 8 (1.8%) & 10 (2.2%) pts treated with ozanimod 0.92 mg, ozanimod 0.46 mg & IFN-β-1a, respectively. Majority of ALT-related TEAEs did not mandate discontinuation, with exception of 4 (0·9%), 1 (0.2%) & 1 (0.2%) pts in the ozanimod 0.92 mg, ozanimod 0.46 mg and IFN-β-1a groups, respectively.

Abbreviations: pt=patients, TEAEs=treatment-emergent adverse events, yr=year, h=hour; HR=heart rate; AV=atrioventricular; ALC=absolute lymphocyte count; ALT: alanine aminotransferase; ULN=upper limit of normal

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- *Ophthalmic:* 3 macular edema cases reported (1 (0.2%)/group), of which 2 (ozanimod 0.46 and 0.92 mg) were confirmed by expert panel review and identified to have predisposing factors unrelated to treatment.[2]
- *Other:* Across groups, the incidences of pulmonary TEAEs (none requiring discontinuation) & depression were low. Malignancies reported in 1 (0.2%), 2 (0.4%), & no pts treated with ozanimod 0.92 mg, ozanimod 0.46 mg & IFN β-1a, respectively

- **RADIANCE** was a Phase 3, multicenter, randomized, double-blind, double-dummy study (N=1,313) that evaluated the efficacy & safety of once-daily oral ozanimod 0.46 mg (n=439) or ozanimod 0.92 mg (n=433) vs. weekly IFN β-1a 30 µg IM injection (n=441) in pts with RMS.[3]
- ARR (primary endpoint) was 0.22 (95% CI, 0.18-0.26) for ozanimod 0.46 mg (21% relative reduction, *P*=.0167) & 0.17 (95% CI, 0.14-0.21) for ozanimod 0.92 mg (38% relative reduction, *P*<.0001) vs. 0.28 (95% CI, 0.23-0.32) for IFN β-1a 30 µg. Dose-dependent effects of ozanimod on ARR vs. IFN β-1a were consistent with the overall primary endpoint across pre-specified subgroups: baseline DMT history (naïve vs. experienced), EDSS subgroups, GdE lesion status (presence vs. absence), sex, & age.
- Both ozanimod 0.46 mg (34% relative reduction, *P*=.0001) & 0.92 mg (42% relative reduction, *P*<.0001) demonstrated a significant reduction in the number of new or enlarging T2 brain lesions over 24 months compared with the IFN β-1a 30 µg group.
- A significant reduction in the number of GdE brain lesions at 24 months was observed with both ozanimod 0.46 mg (47% relative reduction, *P*=.0030) & 0.92 mg (53% relative reduction, *P*=.0006) compared with IFN β-1a 30 µg.
- In a pre-specified pooled analysis of RADIANCE & SUNBEAM, the percentage of pts with 3-month confirmed disability progression was 7.6% (n=67) & 6.5% (n=58) with ozanimod 0.92 mg & 0.46 mg, respectively, & 7.8% (n=69) with IFNβ-1a. No statistically significant difference was observed for either ozanimod groups compared with IFNβ-1a for the key secondary endpoint of 3-month confirmed disability progression.

Safety

- TEAEs were reported in 74.7% (n=324), 74.3% (n=326), & 83.0% (n=365) of pts treated with ozanimod 0.92 mg, ozanimod 0.46 mg, & IFN β-1a, respectively. Most events were mild or moderate.
- Incidence of serious TEAEs was similar across treatment groups Those occurring in more than 1 pt in any group were appendicitis (2 pts in ozanimod 0.92 mg group, 1 in the 0.46 mg group, & 2 in the IFN β-1a group), ovarian cyst (2 in the ozanimod 0.92 mg group), & sinus tachycardia (2 in the ozanimod 0.46 mg group). Posterior reversible encephalopathy syndrome (n=1) was reported ~10 months after ozanimod 0.92 mg initiation in a pt with Guillain-Barré syndrome
- *AEs identified as 'of special interest' in the study, cardiac abnormalities, serious or opportunistic infections, hepatotoxicity, ophthalmic abnormalities, pulmonary abnormalities, depression & malignancies, are summarized below.*
  - *Cardiac:* In first 6h after-ozanimod initiation, greatest decline in mean supine HR was 0.6 bpm at 5h. 4 pts had asymptomatic bradycardia with HR < 45 bpm that resolved & 1 pt had symptomatic bradycardia requiring medical management, but not discontinuation. 2nd/3rd degree AV block TEAEs not reported during study.
  - *Infection*: For the ozanimod 0.92 mg, ozanimod 0.46 mg and IFN-β-1a groups, infection-related TEAEs occurred in 186 (42.3%), 171 (39.0 %) & 182 (41.9%) pts & included herpes infections, which occurred in 9 (2.1), 11 (2.5) & 12 (2.7%) pts, respectively.[4] No serious opportunistic infections occurred.
  - *ALC:* Mean ALC declined at Month 3 post-initiation for ozanimod groups, but stabilized thereafter through Month 24. In the ozanimod 0.92 mg, ozanimod 0.42 mg & IFN-β-1a groups, respectively: mean ALC (% of baseline) at Month 24 was 0.753 (43.2%), 1.012 (54.2%) & 1.833 (98.9%); the mean minimum ALC during the study was 0.525, 0.750, and 1.284. 18 (4·2%) pts with ozanimod 0.92 mg, 4 (0.9%) with ozanimod 0.46 mg & none with IFN-β-1a had an ALC < 2.0, but no associated serious infections occurred.
  - *Hepatic*: ALT rose ≥ 3 x ULN for 29 (6.7%), 26 (5.9%) and 17 (3.9%) pts treated with ozanimod 0.92 mg, ozanimod 0.46 mg and IFN-β-1a, respectively. Majority of ALT-related TEAEs did not mandate discontinuation, with exception of 7 pts (1.6%) treated with ozanimod 0.92 mg, 3 (0.7%) with ozanimod 0.46mg, and 6 (1.4%) with IFN-β-1a.
  - *Ophthalmic*: 5 macular edema cases reported [1 (0.2%) with ozanimod 0.92 mg, 2 (1 (0.2%) each of macular & cystoid) with ozanimod 0.46 mg & 2 (0.5%) with IFN β-1a), of which only 2 (ozanimod 0.46 mg group) confirmed by expert panel review and identified to have preexisting/confounding factors unrelated to treatment.
  - *Other:* Across treatment groups, the incidences of pulmonary TEAEs (none requiring discontinuation) & depression were low. Malignancies reported in 4 (0.9%), 3 (0.7%), & 2 (0.5%) pts treated with ozanimod 0.92 mg, ozanimod 0.46 mg, & IFN β-1a, respectively

Matching Adjusted Indirect Comparison (MAIC) Study

A **MAIC** analysis compared key 1- & 2-yr safety, efficacy & first-dose cardiac monitoring outcomes between ozanimod vs. fingolimod, 2 S1P receptor-modulating agents, for the treatment of RMS pts, adjusting for cross-trial differences in pt data from their pivotal clinical trials.[5]

- Compared with fingolimod, ozanimod was associated with the following significant results:
  - Lower rates of conduction abnormalities (risk difference [RD]: −3.5%) & first-degree AV block (RD: −3.0%), & lower risk of requiring monitoring beyond 6 hours (RD: −8.3%) & of requiring Day 2 monitoring (RD: −2.6%; all *P*<.001).
  - Less reduction in systolic (difference in means: 2.2 mmHg) & diastolic (difference in means: 5.0 mmHg) BP compared with fingolimod at first dose (both *P*<.001). The adjusted absolute increases in the percentages of pts whose lowest hourly recorded heart rate was <45 bpm (range, 45-54) in the first 6 hours were +1.4% (+12.1%) for fingolimod 0.5 mg (*P*<.001), indicating that the adjusted RD was more favorable for ozanimod.
  - Lower risk of any AEs (RD: −9.9%), higher absolute mean lymphocyte count (difference in means: 0.4×10^9/L), & lower risk of abnormal liver enzyme (ALT) elevations (ALT ≥3×ULN; RD: −6.8%) (all P<.05) for the 1-yr adjusted analysis.
  - Lower risk of any AE (RD: −22.7%), AEs leading to discontinuation (RD: −7.4%), herpetic infection (RD: −4.9%), basal cell carcinoma (RD: −1.8%), bradycardia (RD: −0.5%), & abnormal liver enzyme elevations (RD: −3.0%) (all P<.05) for the 2-yr adjusted analysis.
- No significant differences were observed in ARRs between ozanimod & fingolimod at 1-yr & 2-yr adjusted analyses (ARR ratio: 1.08; *P*=.80 & ARR ratio: 1.06; *P*=.78, respectively). Similar % of pts were free of 3-month confirmed disability progression (1-yr analysis: difference in proportions: 1.1%; *P*=.72; 2-yr analysis: difference in proportions: 5.2%; *P*=.12), & 6-month confirmed disability progression (2-yr analysis: difference in proportions: 0.9%; *P*=.76).

Please see Important Safety Information in the cover letter, & accompanying full Prescribing Information & Medication Guide.

References: 1) Zeposia [package insert]. Summit, NJ: Celgene Corporation; March 2020. 2) Comi G, et al. Lancet Neurol. 2019;18(11):1009-1020, 3) Cohen JA, et al. Lancet Neurol. 2019;18(11):1021-1033. 4) Cohen JA, et al. [Supplementary Appendix]. Lancet Neurol. 2019; 18 (11): 1021-1033. 5) Swallow E, et al. J Comp Eff Res. 2020;9(4):275-–285

Abbreviations: pt=patients, TEAEs=treatment-emergent adverse events, yr=year, h=hour; HR=heart rate; AV=atrioventricular; ALC=absolute lymphocyte count; ALT: alanine aminotransferase; ULN=upper limit of normal

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To the members of the Oregon Health Authority formulary committee:

I urge the Oregon Health Authority to add Nurtec to the OHP formulary. Nurtec has the potential to improve the health and quality of life of many of the approximately 500,000 Oregonians afflicted with migraine – a condition that the World Health Organization lists as the seventh most disabling disease worldwide (when a person is in the midst of a major migraine attack they are as unable to function as someone in the midst of a seizure or stroke).

In my 27 years of practicing front line, "in the trenches" neurology in Oregon I have helped care for perhaps two or three thousand migraineurs and have had occasion to use nearly every trick in the book to assist them: a large variety of pharmacotherapies, "electroneuroceuticals" (electronic devices that are FDA approved for treating migraine such as the gammaCore device, Cefaly device, sTMS device, or Nerivio Migra device), botanical supplements, physical therapies, diets, etc. Rarely have I come across a symptomatic/abortificant treatment with the combination of efficacy, tolerability, and safely exhibited by Nurtec.

Nurtec utilizes a novel mechanism of action to rapidly and thoroughly curtail attacks of migraine; not only does it eliminate headache pain but it also ameliorates the major ancillary symptoms of migraine: nausea, photophobia, and sonophobia. Because Nurtec acts through the calcitonin related polypeptide pathway, it is NOT burdened with the safety limitations encumbering the triptan and ergot classes of symptomatic/abortificant anti-migraine medication.

Heretofore triptans and ergots were the mainstay of proper symptomatic/abortificant therapy for acute migraine attacks – but up to a fifth of migraineurs have contraindications to the use of triptans or ergots (such a cerebrovascular disease, cardiovascular disease, hemiplegic migraine, or basilar migraine) and up to half of migraineurs find triptans or ergots to be insufficiently effective or intolerable (even after trying several representatives from each class). The advent of the gepant class of pharmacotherapies promises

significantly better benefit to risk performance. Nurtec in particular has excellent clinical trial data showing rapid onset of action, robust effectiveness in treating several symptoms of migraine attacks concurrently, ease of use, minimal side effects, and excellent safety. I have found that "real life" experience with Nurtec in treating my migraineurs – many of whom are "difficult" migraineurs who have been refractory to several prior therapies – bears out the clinical trial experience: it works and works well.

The rational use of combinations of symptomatic/abortificant and prophylactic therapies for migraine not only results in improved individual outcomes for migraineurs, who will be able to remain productive at work and at home, but also will lower healthcare expenditures in the long run, with fewer emergency room and urgent care clinic visits, lower utilization of rescue medications, and diminished requirements to treat the complications of more troublesome therapies. Not only that, but by improving symptomatic/abortificant treatment of migraine, there will be less impetus to use opioids to treat migraine (which are a terrible choice of treatment for migraine but which far too many healthcare providers are still using for that purpose) – and, of course, if Nurtec can help reduce the use of opioids it will contribute to combating the opioid crisis in our state.

I have been very favorably impressed by how well my migraine patients have responded to Nurtec and I am eager to see it added to Oregon's state formulary. I would be glad to discuss my views on this matter further with any interested parties.

Sincerely,

Walter G. Carlini, MD, PhD
walter.carlini@providence .org
Office telephone: 541-732-8400

From: Jaime Conway, PA-C
Sent: Thursday, July 23, 2020 11:33:46 PM
To: Pharmacy Drug Information
Subject: Medicaid Formulary Consideration for Nurtec ODT

To Whom It May Concern,

I have been practicing in Neurology with a focus in Headache Medicine for the past 5.5 years. The majority of my patients suffer from migraine headache disorders, a highly disabling medical condition which is underrecognized in the medical community.

For many years, triptan medications have been first-line therapy for aborting acute migraine attacks. While these are a reasonable and effective therapy for many of my patients, there are still a large number who are unable to utilize this class of medications, either due to intolerance, inefficacy, or contraindication (cerebrovascular disease, cardiovascular disease, basilar/hemiplegic/complex migraines). Until recently, we were forced to depend on use of butalbital, benzodiazepines, or opioids (nonspecific migraine medications) for these patients, though in very limited quantities due to a great deal of concern that we could ultimately contribute to drug dependence/tolerance, the opioid crisis, and/or worsening of their headache syndrome with inducing rebound/medication overuse headaches. However, with the recent FDA approval of Nurtec ODT, I am very pleased to be transitioning many of my patients away from these offensive medications and towards a migraine-specific therapy which they have previously been unable to access.

In my experience thus far with the new gepant class of medications, the majority of my patients experience a positive response. It is notable, however, that I much prefer Nurtec ODT over Ubrelvy for a variety of reasons:

1. ODT formulation rather than tablet (as gastric stasis is frequently problematic during acute migraine attacks)
2. Longer half-life (which breaks migraine headache cycles/status migrainosus more effectively than a shorter half-life)
3. More favorable side effect profile

All things considered, I would appreciate your consideration for adding Nurtec ODT to Medicaid formulary.

If you have any questions or concerns, please feel free to reach out to me directly via email or contacting my office at extension 731.

Thank you,

Jaime Conway, MPAS, PA-C

Headache Center at Piercey Neurology LLC
305 SW C Avenue
Corvallis, OR 97333
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From: Perez, Harold
Sent: Monday, August 3, 2020 12:13:27 PM
To: Pharmacy Drug Information
Subject: Nurtec ODT

Good Afternoon,

I am a Primary Care Physician Specialized in Family Medicine and am sending this email in support of having this new acute migraine medication as an option for my OHP patients. I have a number of patients who would benefit from this class of medication for their acute migraine treatment including patients that do not respond or tolerate Triptans or patients with a contraindication for Triptans because of Cardiovascular Disease. It is also another alternative to move some patients away from Opioids as their main headache treatment.
Thanks for the consideration.

Harold Perez MD.
Oregon Medical Group