Early Intervention in SMA
How Access to Therapy Will Alter Disease Management As We Know It

Unraveling Autoimmune Epilepsy

Addressing the Invisible Symptoms of Parkinson Disease

Closing the Treatment Gap in Progressive MS

Selective Inverse Agonists of the Histamine 3 Receptor as Treatment for Narcolepsy

CLINICAL VIEWPOINT
Telemedicine, Technology, and the Future of Alzheimer and Dementia Care
WITH HOWARD FILLIT, MD

NEUROLOGYLIVE.COM
ZEOSIA® (ozanimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

**Indication**
ZEOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

**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:** ZEOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEOSIA. 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 ZEOSIA. Delay initiation of ZEOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEOSIA.
- Herpes zoster was reported as an adverse reaction in ZEOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine-1-phosphate (SIP) 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 ZEOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEOSIA.
- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another SIP receptor modulator. If CM is suspected, ZEOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

**DISCOVER THE FIRST AND ONLY SIP WITH NO FIRST-DOSE OBSERVATION REQUIRED**

**FULL PRESCRIBING INFORMATION FOR ZEOSIA HAS NO FDO REQUIRED, NO GENETIC TESTING REQUIRED, AND NO OPHTHALMIC TESTING REQUIRED FOR MOST PATIENTS**

Start at ZEOSIAhcp.com
ZEPOSIA is commercially available in the US as of June 1, 2020, following FDA approval on March 25, 2020.

Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations. Patients without a confirmed history of varicella (chickenpox), or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation. For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.

Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.

Study designs: SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg weekly Avonex (interferon beta-1a), 30 μg intramuscular injection. Primary endpoint: ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). Secondary endpoints: ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.

A relapse was defined as the occurrence of new or worsening neurological symptoms persistent for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.

Adverse reactions: Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year were 59.8% and 75.5%, respectively, and at 2 years were 74.7% and 85.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of ≥2% for ZEPOSIA vs Avonex, respectively, were as follows: nasopharyngitis, 11.1% (vs 9.5%); alanine aminotransferase increased, 5.3% (vs 3.2%); gamma-glutamyl transferase increased, 4.5% (vs 1.2%); urinary tract infection, 4.1% (vs 3.1%); hypertension, 3.4% (vs 2.0%); pharyngitis, 3.2% (vs 2.3%); and respiratory tract infection viral, 2.4% (vs 1.2%). Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. Serious infections: The rate of serious infections at 1 year for ZEPOSIA was 1.0% vs 0.6% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. Malignancy rates: The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.

ALC: ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of reversible retention of lymphocytes in lymphoid tissues. ZEPOSIA may therefore increase the susceptibility to infections. Mean ALC was 0.75 × 10^9 cells/L for both SUNBEAM and RADIANCE (at 1 year and 2 years, respectively).

ALC=absolute lymphocyte count; ARR=annualized relapse rate; CBC=complete blood count; ECG=electrocardiogram; FDO=first-dose observation; GdE=gadolinium enhancing; S1P=sphingosine-1-phosphate; VZV=varicella-zoster virus.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (CONTINUED):

- 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 Ia 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.
IMPORTANT SAFETY INFORMATION (CONTINUED)

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 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.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information.

ZEPOSIA® (ozanimod) capsules, for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE
ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 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 (CBC), including lymphocyte count [see Warnings and Precautions (5.1)].

Cardiac Evaluation
Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought [see Warnings and Precautions (5.2)].

Liver Function Tests
Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels [see Warnings and Precautions (5.3)].

Ophthalmic Assessment
In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula [see Warnings and Precautions (5.7)].

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 [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].
- Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction [see Warnings and Precautions (5.2) and Drug Interactions (7.2)].

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 [see Warnings and Precautions (5.1) and Drug Interactions (7.3)]. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

2.2 Dosing Information
Maintenance Dosage
After initial titration (see Treatment Initiation), 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 1 [see Warnings and Precautions (5.2)].

<table>
<thead>
<tr>
<th>Days</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>0.23 mg once daily</td>
<td></td>
</tr>
<tr>
<td>5-7</td>
<td>0.46 mg once daily</td>
<td></td>
</tr>
<tr>
<td>8 and thereafter</td>
<td>0.92 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

2.3 Reinitiation 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 (see Dosage and Administration (2.2)).

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

4 CONTRAINDICATIONS
ZEPOSIA is contraindicated in patients who:

- In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure [see Warnings and Precautions (5.2)].
- Have the presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker [see Warnings and Precautions (5.2)].
- Have severe untreated sleep apnea [see Warnings and Precautions (5.2)].
- Are taking a monoamine oxidase (MAO) Inhibitor [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections
Risk of Infection

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2)]. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. 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. In Study 1 and Study 2, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA was similar to that in patients who received interferon (IFN) beta-1a (50% vs 34% and 1% vs 0.8%, respectively). ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster [see Adverse Reactions (6.1)].

The proportion of patients who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.3%. These values generally returned to greater than 0.2 x 10^9/L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)].

Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Because the elimination of ZEPOSIA after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

Hepatic Viral Infection
In Study 1 and Study 2, hepatic zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients who received IFN beta-1a. Hepatic simplex encephalitis and varicella zoster meningitides have been reported with sphingosine 1-phosphate (SIP) receptor modulators. Patients without a healthcare professional-conferred 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 [see Vaccinations below].

Cryptococcal Infection
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with SIP receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leuкоencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. 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.

PML has been reported in patients treated with SIP receptor modulators and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). 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 ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

If PML is confirmed, treatment with ZEPOSIA should be discontinued.

Prior and Concomitant Treatment with Anti-neoplastic, Immunosuppressive, or Immune-modulating Therapies
In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for the treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Vaccinations
Patients without a healthcare professional-conferred history of chickenpox or without documentation of a full course of vaccination against 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, following which initiation of treatment with ZEPOSIA should be postponed for 4 weeks to allow the full effect of vaccination to occur.

No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations may be less effective if administered during ZEPOSIA treatment.

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA.

5.2 Bradycardyhy and Atrioventricular Conduction Delays
Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)].

ZEPOSIA was not studied in patients who had:

- A myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months
- New York Heart Association Class III / IV heart failure
- Cardiac conduction or rhythm disorders, including sick sinus syndrome, significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that in the opinion of the treating investigator could jeopardize the patient’s health
- Other or uncontrolled cardiac conditions without clearance from a cardiologist
- Severe untreated sleep apnea
- A resting heart rate less than 55 beats per minute (bpm) at baseline

Reduction in Heart Rate
Initiation of ZEPOSIA may result in a transient decrease in heart rate. In Study 1 and Study 2, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued once-daily up-titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in the clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed.

Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
In Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

5.3 Liver Injury
Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA.

In Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2-4 weeks in clinical trials.

In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

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 ZEPOSIA should be discontinued if significant liver injury is confirmed.

Individuals with an ALT or AST greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

5.4 Fetal Risk
There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm [see Use in Specific Populations (8.1)]. Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for at least 4 weeks after stopping ZEPOSIA [see Use in Specific Populations (8.1)].

5.5 Increased Blood Pressure
In Study 1 and Study 2, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over patients who received IFN beta-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment and persisted throughout treatment. Hypertension was reported as an adverse reaction in 3.9% of patients treated with ZEPOSIA 0.92 mg in 2.1% of patients who received IFN beta-1a.

Two patients treated with ZEPOSIA in Study 1 and one patient treated with interferon (IFN) beta-1a in Study 2 experienced a hypertensive crisis that was not clearly influenced by a concomitant medication. Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.

Certain foods that may contain very high amounts (i.e., more than 150 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even at the recommended doses. Because of an increased sensitivity to tyramine, patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

5.8 Respiratory Effects
Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with ZEPOSIA as early as 3 months after treatment initiation. In pooled analyses of Study 1 and Study 2, the decline in FEV1 started before treatment initiation. At baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and %predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a (60 mL, 95% CI (-110, -10), 1.4%, 95% CI: (-2.6, -0.2)), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. One patient discontinued ZEPOSIA because of dyspnea. Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

5.7 Macular Edema
S1P modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA.

Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.8 Posterior Reversible Encephalopathy Syndrome
RARE cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortic visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. 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.

5.9 Unintended Additive Immunosuppressive Effects
When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating ZEPOSIA.

Initiating treatment with ZEPOSIA after treatment with alentuzumab is not recommended [see Drug Interactions (7.1)].

5.10 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. Patients should be observed for a severe increase in disability upon ZEPOSIA discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping ZEPOSIA
After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)]. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Infections [see Warnings and Precautions (5.1)]
- Bradycardia and Atioventricular Conduction Delays [see Warnings and Precautions (5.2)]
- Liver Injury [see Warnings and Precautions (5.4)]
- Fetal Risk [see Warnings and Precautions (5.4)]
- Increased Blood Pressure [see Warnings and Precautions (5.5)]
- Respiratory Effects [see Warnings and Precautions (5.6)]
- Macular Edema [see Warnings and Precautions (5.7)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs [see Warnings and Precautions (5.9)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ZEPOSIA was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA 0.92 mg [see Clinical Studies (14)].

Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than comparator. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received IFN beta-1a were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.
Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a (Pooled Study 1 and Study 2)

| Adverse Reactions                           | Studies 1 and 2 | IFN beta-1a
|--------------------------------------------|----------------|-------------------
|                                            | ZEPOSIA 0.92 mg (n=882) | 30 mcg Intramuscularly Once Weekly (n=885) |
|                                            | %             | %                |
| Upper respiratory infection                | 26            | 23               |
| Hepatic transaminase elevation             | 10            | 5                |
| Orthostatic hypotension                    | 4             | 3                |
| Urinary tract infection                    | 4             | 3                |
| Back pain                                  | 4             | 3                |
| Hypertension                               | 4             | 2                |
| Abdominal pain upper                       | 2             | 1                |

* Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.

7.7 Monoamine Oxidase (MAO) Inhibitors
Co-administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod may inhibit MAO [see Clinical Pharmacology (12.3)]. The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis. Therefore, co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.

7.8 Adrenergic and Serotonergic Drugs
Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis. Therefore, co-administration of ZEPOSIA with drugs or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures (see Data). The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation

There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rats at levels higher than those in maternal plasma.
INFECTIONS

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

8.3 Females and Males of Reproductive Potential

Contraception

Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with ZEPOSIA (see Use in Specific Populations (8.1)). Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping ZEPOSIA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown (see Clinical Pharmacology (12.3)). Use of ZEPOSIA in patients with hepatic impairment is not recommended.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg.rasH2 mice for 26-weeks resulted in an increase in hemangio- and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to rats for 2 years resulted in no increase in tumors. At the highest dose tested (2 mg/kg/day), plasma exposure (AUC) for ozanimod was approximately 100 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Mutagenesis

Ozanimod was negative in a battery of in vitro (Ames, mouse lymphoma tk) and in vivo (rat micronucleus/comet) assays. Metabolite CC112273 was negative in in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vitro chromosomal aberration assay in human (TK6) cells but negative in an in vivo rat micronucleus/comet assay.

Impairment of Fertility

Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and continuing through gestation day 7 resulted in no adverse effects on fertility. At the highest dose tested (30 mg/kg/day), plasma ozanimod exposure (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) (0.92 mg/day); plasma AUCs for metabolites, CC112273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Infections

Inform patients that they may be more likely to get infections, some of which could be life-threatening, when taking ZEPOSIA and for 3 months after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection (see Warnings and Precautions (5.1)). Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection. Advise patients that some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with ZEPOSIA. If immunizations are planned, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA. Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA.

Cardiac Effects

Advise patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate. Inform patients that to reduce this effect, dose titration is required. Advise patients that the dose titration is also required if a dose is missed for 1 day or more during the first 14 days of treatment (see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)).

Liver Injury

Inform patients that ZEPOSIA may increase liver enzymes. Advise patients that they should contact their healthcare provider if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine (see Warnings and Precautions (5.3)).

Pregnancy and Fetal Risk

Inform patients that, based on animal studies, ZEPOSIA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with ZEPOSIA and for 3 months after stopping ZEPOSIA. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant (see Warnings and Precautions (5.4)).

Respiratory Effects

Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea (see Warnings and Precautions (5.6)).

Macular Edema

Advise patients that ZEPOSIA may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema maybe increased (see Warnings and Precautions (5.7)).

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological consequences (see Warnings and Precautions (5.8)).

Severe Increase in Disability After Stopping ZEPOSIA

Inform patients that severe increase in disability has been reported after discontinuation of a S1P receptor modulator like ZEPOSIA. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of ZEPOSIA (see Warnings and Precautions (5.10)).

Immune System Effects After Stopping ZEPOSIA

Advise patients that ZEPOSIA continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 months after the last dose (see Warnings and Precautions (5.11)).
Early Intervention in SMA: How Access to Therapy Will Alter Disease Management As We Know It

BY KENNETH BENDER, PHARMD, MA

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INDICATIONS AND USAGE
FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION
- There is an association between serotoninergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension.
- Echocardiogram assessments are required before, during, and after treatment with FINTEPLA.
- FINTEPLA is available only through a restricted program called the FINTEPLA REMS.

CONTRAINDICATIONS
FINTEPLA is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients in FINTEPLA and with concomitant use of, or within 14 days of, the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome.

WARNINGS AND PRECAUTIONS
Valvular Heart Disease and Pulmonary Arterial Hypertension (see Boxed Warning): Because of the association between serotoninergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension, cardiac monitoring via echocardiogram is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can aid in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease or pulmonary arterial hypertension.

Monitoring: Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease and pulmonary arterial hypertension. Echocardiograms should be repeated every 6 months, and once at 3-6 months post treatment with FINTEPLA.

If valvular heart disease or pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA REMS Program (see Boxed Warning): FINTEPLA is available only through a restricted distribution program called the FINTEPLA Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified by enrolling in the FINTEPLA REMS. Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment. Patients must enroll in the FINTEPLA REMS and comply with ongoing monitoring requirements. The pharmacy must be certified by enrolling in the FINTEPLA REMS and must only dispense to patients who are authorized to receive FINTEPLA. Wholesalers and distributors must only distribute to certified pharmacies. Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

Decreased Appetite and Decreased Weight: FINTEPLA can cause decreases in appetite and weight. Decreases in weight appear to be dose related. Most patients resumed the expected measured increases in weight by the end of the open-label extension study. Weight should be monitored regularly during treatment with FINTEPLA and dose modifications should be considered if a decrease in weight is observed.

Somnolence, Sedation, and Lethargy: FINTEPLA can cause somnolence, sedation, and lethargy. Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on
Profound seizure reduction can leave more room for life’s little victories.

Among patients taking FINTEPLA 0.7 mg/kg/day over 14 weeks*:

- 58% of patients had a profound (275%) reduction in convulsive seizures vs 3% in the placebo group (P<.001)
- 50% of patients achieved a seizure-free (0 seizures) interval lasting at least 21 days vs 8 days in the placebo group (P<.001)

In this 14-week trial, the placebo-adjusted percent reduction in monthly convulsive seizure frequency was 70.0% for FINTEPLA 0.7 mg/kg/day (P<.001) and 31.7% for FINTEPLA 0.2 mg/kg/day (P=.043)

FINTEPLA is to be administered orally and may be taken with or without food. The starting dose is 0.1 mg/kg twice daily, which can be increased based on efficacy and tolerability

- The maximum daily maintenance dose of FINTEPLA is 0.35 mg/kg twice daily, not to exceed a total daily dose of 26 mg. When FINTEPLA is coadministered with stiripentol plus clobazam, with or without valproate, the maximum daily maintenance dose of FINTEPLA is 0.2 mg/kg twice daily, not to exceed a total daily dose of 17 mg

*The safety and effectiveness of FINTEPLA for the treatment of seizures associated with Dravet syndrome were established in 2 randomized, double-blind, placebo-controlled trials in 202 patients 2 to 18 years of age. Study 1 (N=117) compared 0.7 and 0.2 mg/kg/day FINTEPLA with placebo in patients who were inadequately controlled on 1-4 concomitant antiepileptic drugs and had a minimum of 6 convulsive seizures during the baseline period. The primary efficacy endpoint was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) titration and maintenance periods (ie, treatment period). The median longest interval between convulsive seizures was also assessed.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont.)

FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behaviors in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risks of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviors. Should suicidal thoughts and behaviors emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Withdrawal of Antiepileptic Drugs: As with most AEDs, FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly during concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (eg, St. John’s Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA), dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

Increase in Blood Pressure: FINTEPLA can cause an increase in blood pressure. Significant elevation in blood pressure, including hypertensive crisis, has been reported rarely in adult patients treated with fenfluramine, including patients without a history of hypertension. Monitor blood pressure in patients treated with FINTEPLA. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed hypertensive crisis.

Glaucoma: Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder; gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

DRUG INTERACTIONS

Strong CYP1A2 and CYP2B6 Inducers: Coadministration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations. Consider an increase in FINTEPLA dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer.

USE IN SPECIFIC POPULATIONS

Administration to patients with moderate or severe renal impairment or to patients with hepatic impairment is not recommended.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on the following page.
**Brief Summary of FULL PRESCRIBING INFORMATION**

**FINTEPLA®** (fenfluramine) oral solution, GIV

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**WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION**

There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The benefits versus the risks of initiating or continuing FINTEPLA must be considered, based on echocardiogram findings. Because of the risks of valvular heart disease and pulmonary arterial hypertension, FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS.

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**CONTRAINDICATIONS**

FINTEPLA is contraindicated in patients with:

- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA
- Concomitant use of, or within 14 days of the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome

**WARNINGS AND PRECAUTIONS**

**Valvular Heart Disease**

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA. Cardiac monitoring via echocardiogram can identify evidence of valvular heart disease prior to a patient becoming symptomatic, aiding in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease.

**Monitoring**

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

If valvular heart disease is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA is available only through a restricted program under a REMS.

**Pulmonary Arterial Hypertension**

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and pulmonary arterial hypertension, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can identify evidence of pulmonary arterial hypertension prior to a patient becoming symptomatic, aiding in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed pulmonary arterial hypertension.

**Monitoring**

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for pulmonary arterial hypertension.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

If pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA is available only through a restricted program under a REMS.

**FINTEPLA REMS Program**

FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension.

Notable requirements of the FINTEPLA REMS Program include:

- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive FINTEPLA.
- Wholesalers and distributors must only distribute to certified pharmacies.

Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

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**Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events per 1000 Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

**Withdrawal of Antiepileptic Drugs**

As with most AEDs, FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.
Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotoninergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SSRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), bupropion, triptans, dietary supplements (e.g., St. John’s Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), which are contraindicated with FINTEPLA), dex trimethorphan, lithium, tramadol, and antipsychotics with serotoninergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

Increase in Blood Pressure

FINTEPLA can cause an increase in blood pressure. Significant elevation in blood pressure, including hypertensive crisis, has been reported rarely in adult patients treated with fenfluramine, including patients without a history of hypertension. Monitor blood pressure in patients treated with FINTEPLA. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed a hypertensive crisis.

Glaucome

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Valvular Heart Disease
- Pulmonary Arterial Hypertension
- Decreased Appetite and Decreased Weight
- Somnolence, Sedation, and Lethargy
- Suicidal Behavior and Ideation
- Withdrawal of Antiepileptic Drugs
- Serotonin Syndrome
- Increase in Blood Pressure
- Glaucome

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with Dravet syndrome, 341 patients were treated with FINTEPLA, including 312 patients treated for more than 6 months, 294 patients treated for more than 1 year, and 138 patients treated for more than 2 years.

In placebo-controlled trials of patients with Dravet syndrome, 122 patients were treated with FINTEPLA. The duration of treatment in these trials was 16 weeks (Study 1) or 17 weeks (Study 2). In Study 1 and Study 2, the mean age was 9 years (range 2 to 19 years) and approximately 46% of patients were female and 74% were White. All patients were receiving at least one other AED.

In Study 1 and Study 2, the rate of discontinuation as a result of any adverse reaction were 13%, 0%, and 7% for patients treated with FINTEPLA 0.7 mg/kg/day, 0.2 mg/kg/day, and 0.4 mg/kg/day in combination with stiripentol, respectively, compared to 6% for patients on placebo. The most frequent adverse reaction leading to discontinuation in the patients treated with any dose of FINTEPLA was somnolence (n=3, 3%).

The most common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram, fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

Table 3 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 1 and Study 2.

### Table 3: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Combined Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>23%</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>Somnolence, sedation, lethargy</td>
<td>26%</td>
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<td>23%</td>
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<tr>
<td>Abnormal echocardiogram</td>
<td>18%</td>
<td>23%</td>
<td>9%</td>
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<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>5%</td>
<td>23%</td>
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<tr>
<td>Constipation</td>
<td>3%</td>
<td>10%</td>
<td>7%</td>
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<tr>
<td>Fatigue, malaise, asthenia</td>
<td>15%</td>
<td>10%</td>
<td>30%</td>
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<tr>
<td>Ataxia, balance disorder, gait disturbance</td>
<td>10%</td>
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<tr>
<td>Blood pressure increased</td>
<td>13%</td>
<td>8%</td>
<td>0%</td>
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<tr>
<td>Drooling, salivary hypersecretion</td>
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<td>Hypotonia</td>
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<td>Rash</td>
<td>8%</td>
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<tr>
<td>Blood prolactin increased</td>
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<tr>
<td>Chills</td>
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<td>5%</td>
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<tr>
<td>Decreased activity</td>
<td>0%</td>
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<tr>
<td>Dehydration</td>
<td>0%</td>
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<tr>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Weight decreased</td>
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<td>5%</td>
<td>7%</td>
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<td>Grou</td>
<td>5%</td>
<td>3%</td>
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<td>3%</td>
<td>9%</td>
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<td>2%</td>
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<tr>
<td>Increased heart rate</td>
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<td>3%</td>
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<tr>
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<td>Rhinitis</td>
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<tr>
<td>Tremor</td>
<td>3%</td>
<td>3%</td>
<td>9%</td>
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<tr>
<td>Urinary incontinence</td>
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<td>3%</td>
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<tr>
<td>Decreased blood glucose</td>
<td>0%</td>
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<td>9%</td>
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<tr>
<td>Bronchitis</td>
<td>3%</td>
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<td>9%</td>
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<tr>
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<td>Eczeema</td>
<td>0%</td>
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<td>Enuresis</td>
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<tr>
<td>Fall</td>
<td>3%</td>
<td>0%</td>
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<tr>
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<td>0%</td>
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<tr>
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<td>0%</td>
<td>5%</td>
<td>0%</td>
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<tr>
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<td>5%</td>
<td>0%</td>
<td>0%</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Viral infection</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
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</tbody>
</table>

(1) 0.4 mg/kg/day was not an intermediate dose. Patients on the 0.4 mg/kg/day dose were also taking concomitant stiripentol plus clobazam, which increases exposure of FINTEPLA.

(2) Patients in placebo groups from Studies 1 and 2 were pooled.

(3) Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic.

### Echocardiographic Safety Assessments of Valvular Heart Disease and Pulmonary Arterial Hypertension

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for up to 3 years in duration.

No patient developed echocardiographic findings consistent with either valvular heart disease or pulmonary arterial hypertension in the placebo-controlled studies or during the open-label extension study of up to 3 years in duration. In Study 1 and Study 2, 16% of patients taking FINTEPLA compared to 6% of patients taking placebo were reported to have trace mitral regurgitation, and 3% of patients taking FINTEPLA and not patients taking placebo were found to have trace aortic regurgitation. During the open-label extension study, trace mitral regurgitation and trace aortic regurgitation were reported in 1% and 0.4%, respectively, of patients taking FINTEPLA. Trace and mild mitral regurgitation, and trace aortic regurgitation are considered physiologic in the absence of structural valve abnormalities.
**DRUG INTERACTIONS**

**Effect of Other Drugs on FINTEPLA**

**Stiripentol Plus Clobazam**

Coadministration of FINTEPLA with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations and decreases its metabolite, norfenfluramine, because of the inhibition of the metabolism of fenfluramine. If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg).

**Strong CYP1A2 and CYP2B6 Inducers**

Coadministration with rifampin or strong CYP1A2 and CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA.

**Consider an increase in FINTEPLA dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer; however, do not exceed the maximum daily dosage.**

**Effects of Serotonin Receptor Antagonists**

Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of FINTEPLA. If cyproheptadine or potent 5-HT1A, 5-HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are coadministered with FINTEPLA, patients should be monitored appropriately.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FINTEPLA, during pregnancy. Encourage women who are taking FINTEPLA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

**Risk Summary**

There are no adequate human or animal data on the developmental risks associated with the use of FINTEPLA in pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown.

**Lactation**

**Risk Summary**

There are no data on the presence of fenfluramine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for FINTEPLA and any potential adverse effects on the breastfed infant from FINTEPLA or from the underlying maternal condition.

**Pediatric Use**

The safety and effectiveness of FINTEPLA for the treatment of seizures associated with Dravet syndrome have been established in patients 2 years of age and older.

Safety and effectiveness in patients less than 2 years of age have not been established.

**Juvenile Animal Data**

Oral administration of fenfluramine (0.3, 3.5, 9, or 20 mg/kg/day) to young rats for 10 weeks starting on postnatal day 7 resulted in reduced body weight and neurobehavioral changes (decreased locomotor activity and learning and memory deficits) at all doses tested.

Neurobehavioral effects persisted after dosing was discontinued. Bone size was decreased at the mid and high doses; brain size was decreased at the highest dose. Partial or complete recovery was seen for these endpoints. A no-effect dose for postnatal developmental toxicity was not identified. The lowest dose tested (3.5 mg/kg/day) was associated with plasma fenfluramine exposures (AUG) less than that in humans at the maximum recommended human dose (MRHD) of 30 mg/day and norfenfluramine (metabolite) exposures (AUG) approximately 3 times that in humans at the MRHD.

**Geriatric Use**

Clinical studies of FINTEPLA for the treatment of Dravet syndrome did not include patients 65 years of age and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Renal Impairment**

Administration of FINTEPLA to patients with moderate or severe renal impairment is not recommended.

**Hepatic Impairment**

Administration of FINTEPLA to patients with hepatic impairment is not recommended.
FROM THE CHAIRMAN

Making Nonpersonal Learning Personal in the Age of COVID-19

THE PRINCIPLES OF HEALTH CARE are built on pillars of education—a need to constantly work to understand more so that we may do more. In many ways, the coronavirus disease 2019 (COVID-19) pandemic has bolstered education by creating an immediate need for more research, as the unknowns of the virus continue to ignite inquiries across medicine.

The same reasons why bench-to-bedside progress is being made in this space are also responsible for weakening support or interest in topics not related to COVID-19—topics that remain immensely important to the ongoing care of patients, especially those with chronic neurological diseases.

Efforts to advance our understanding and management of these conditions have been stifled by restrictions put forth by the pandemic, severely limiting opportunities to gather and share information and experiences. Although many societies and organizations have worked tirelessly to pivot their annual meetings and educational seminars to virtual offerings, we understand that it’s hard to replace the value of seeing and speaking with your peers and mentors in person.

With a strong background of video-based educational programs, MJH Life Sciences™ and NeurologyLive® have been quick to adapt to this changing environment in hopes of not only preserving some of those benefits, but also broadening your ability to learn and grow your practice.

In May, NeurologyLive® partnered with the Consortium of Multiple Sclerosis Centers (CMSC) to pivot their annual educational event to a multiday virtual conference. The 2020 CMSC Virtual Annual Meeting featured 18 accredited presentations from leaders in the field on an easy-to-access platform supported by additional conference coverage that you’ve come to expect from NeurologyLive®.

In addition to continuing our high-value coverage of the latest research, we also pivoted our popular Peer Exchange and Insights programs to virtual formats, taking advantage of having no physical barriers by incorporating more varied perspectives. In our Peer Exchange titled, “Global Approaches to the Management of Relapsing Multiple Sclerosis,” we brought together 4 global experts to share how differences in international guidelines and therapies affect their treatment decisions.

This fall, we will continue to provide you with valuable remote learning opportunities through our 2nd Annual International Congress on the Future of Neurology®, which will bring together experts from multiple neurology subspecialties to share unique perspectives on hot topics in epilepsy, dementia, sleep disorders, movement disorders, and more.

You can continue to count on NeurologyLive® to provide you with a multitude of opportunities to grow as a health care provider through access to valuable, expert-driven resources—whether you’re tuning in from your home office or joining us in person.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

NeurologyLive.com
WE ARE IN A TIME OF unbearable uncertainty, and the field of medicine is being alternately vilified and sanctified in the court of public opinion. As physicians, over the past 100-plus days we have had to adapt our practices to focus on the public health emergency at hand, but we are also acutely aware that the rest of our patients’ comorbidities have not stopped during the coronavirus disease 2019 (COVID-19) pandemic. In some cases, just the context of the pandemic and quarantine have made patients more symptomatic. Keeping abreast of emerging treatments and expanding our understanding of underlying disease states must continue. In this issue of NeurologyLive® we look at chronic conditions such as Parkinson disease (PD) and epilepsy through a new lens, learn more about the mysteries of narcolepsy, examine whether the repurposing of new meds can help with multiple sclerosis (MS), and provide greater understanding of the frustrating frontiers of gene therapy for spinal muscular atrophy.

PD psychosis impacts up to 50% of patients with PD. As a movement disorder specialist, I have been dealing with this in my clinic for years, and now I am dealing with it remotely through a computer monitor in the age of telemedicine during the public health emergency. It is frustrating for patients, families, and physicians under the best of circumstances, and I can relate with complete confidence that you do not need to have contracted COVID-19 to be a victim of this pandemic. PD psychosis and other behavioral issues in PD are increasing with the pandemic and quarantine have made patients more symptomatic. Whether seeing new patients or follow-up patients, chances are that of these visits are conducted via computer or phone. Telehealth technology has been in place for decades and its incorporation into clinical practice was stunted primarily due to lack of service and payment parity as recognized by commercial, state, and federal insurance. Through the CARES (Coronavirus Aid, Relief, and Economic Security) Act waiver, these restrictions were lifted and telehealth platforms were adopted across all practice types. The utility, improved access, and provider and patient satisfaction reports cannot be ignored.

Narcolepsy is a fascinating sleep disorder. Our article Selective Inverse Agonists of the Histamine 3 Receptor as Treatment for Narcolepsy on page 40 delves into the pathophysiology of the disorder to highlight new, potentially more effective therapies on the horizon that focus on modulating histamine pathways; these are very different from the traditional psychostimulant medications that have been used. In 2019, Farmer was elected president of the Philadelphia Neurological Society and also coordinates the Delaware Valley Regional Movement Disorder Meeting.

Multiple sclerosis (MS) has seen a flurry of new disease-modifying therapies for those with a relapsing-remitting course. There is new hope on the horizon to use these therapies for primary and secondary progressive MS, variations of the condition that have sorely lacked effective treatment. In Closing the Treatment Gap in Progressive MS on page 63, we explore how ocrelizumab may fulfill this promise.

Lastly, our cover story Early Intervention in SMA: How Access to Therapy Will Alter Disease Management As We Know It on page 36 is a timely piece that exposes how available treatments are at the mercy of state laws and practices. Spinal muscular atrophy (SMA) is the leading genetic cause of infant mortality, so it may be shocking to learn that now with 2 FDA-approved lifesaving treatments, and a third in development, universal newborn screening has still not been mandated across all states. This is an area of advocacy that predates the public health emergency, but there are echoes that can be heard in advocacy born of the pandemic: advocacy for telehealth.

Whether seeing new patients or follow-up patients, chances are that if you have continued to practice during the pandemic, a large majority of these visits are conducted via computer or phone. Telehealth technology has been in place for decades and its incorporation into clinical practice was stunted primarily due to lack of service and payment parity as recognized by commercial, state, and federal insurance. Through the CARES (Coronavirus Aid, Relief, and Economic Security) Act waiver, these restrictions were lifted and telehealth platforms were adopted across all practice types. The utility, improved access, and provider and patient satisfaction reports cannot be ignored. Survey studies conducted during the pandemic through Alliance for Connected Care captured the shift in culture with unsurprising results:

- A March survey found that 59% of US consumers surveyed said they are more likely to use telehealth services now than previously, and 36% said they would switch their physician in order to have access to virtual care.
FROM THE EDITOR

It is imperative to advocate for telemedicine’s continued use as an option for patients during the public health emergency and beyond.

—JILL GIORDANO FARMER, DO, MPH

• A new poll of more than 1000 seniors found that 52% are comfortable using telehealth to receive health care. Of those who have used telehealth during the pandemic, 91% reported a favorable experience, and 78% are likely to complete a medical appointment via telehealth again in the future.
• A recent survey found that health system CEOs foresee a wave of innovation in telehealth over the next year. In addition, 92.9% of CEOs cited telehealth as a technology with the most potential to support response to the COVID-19 pandemic.
• A survey of more than 1300 physicians found that more than 90% are treating some or all of their patients via telehealth. Additionally, about 60% of physicians who are currently using telemedicine tools during the public health emergency said they plan to use telemedicine more often than they did before COVID-19.

What is also predictable is that commercial and governmental payers have already reinstated some restrictions to the reimbursement for telemedicine. It is imperative to advocate for its continued use as an option for patients during the public health emergency and beyond. If you are interested in learning more about advocacy efforts, please refer to NeurologyLive® online where you can download a letter to send to your representatives.

I want to thank you for taking a break from your daily deluge of information and spending some time with NeurologyLive®. Although it was crafted in the context of the ongoing public health emergency and there are some aspects of this issue that may be directly applicable to it, I hope that other articles can help give you a moment to relax, reload, think about something else, and learn something new.

Stay well,
Jill Farmer, DO, MPH

REFERENCE
http://www.connectwithcare.org/studies-reports/

NeurologyLive.com
5 CARE TRANSITION TAKEAWAYS FROM COVID-19

BY B.J. BOYLE

ALTHOUGH THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic has created unprecedented challenges for health care providers, it has also revealed valuable lessons to help us navigate these turbulent times. The following 5 key takeaways will enable providers to develop better care transitions for their patients and prepare for what lies ahead:

1. Clear, concise, consistent communication is critical.
Regardless of the state of business or the world around it, sharing information with employees, patients, their families, and others in the care spectrum is essential. Although it sounds simple and straightforward, many health care providers and operators have learned during the pandemic that it was anything but.

“Originally, we overwhelmed ourselves and our clients by sending too much information, without first curating it,” said April Catterton, BSN, RN, PCS manager of myPotential at Home, in Winchester, Virginia. “Now we understand that first establishing a clear message and then sharing it across the entire organization is a number-1 priority.”

Rather than responding on the fly, health care providers benefit from taking a step back, confirming information and sources, and working to deliver sound messages in a timely manner.

“Increase the level of one-on-one and group communication to ensure you’re on the same page, allocate resources appropriately, and make it as seamless as possible for clients and staff to communicate,” said Catterton. “If you’re managing a highly contagious infection, you should be going through the same processes of communication each and every time.”

2. Walk before you run.
During a crisis, there’s a tendency to attempt to cover all bases at once. Organizations under fire realize that they can move far faster than they normally do, and they often do it without first covering the basics. This scattered approach doesn’t work.

“We learned that there’s no need to overcomplicate it,” Erin Devine, director of quality and community partnership for the University of Cincinnati, said. “We rushed to put so many things in place when what we really needed to do was to focus on the basics.”

Start at the beginning by ensuring your skilled partners have the assistance they need, assistance as simple as support for infection control and the right amount of personal protective equipment.

3. Informed decisions depend on data.
Looking at past data allows organizations to spot trends, predict outcomes, and formulate more effective plans. However, dealing with COVID-19, an unprecedented crisis, meant there was no looking back for guidance.

Providers navigating the pandemic relied on live, real-time data, including COVID-19–positive patients, pending test results, patient risks, emergency medical service calls, ventilator counts, and intensive care unit (ICU) rates. Those data allowed teams to move equipment and support, rather than people, ensuring safer, more comfortable care transitions.

Some, like Tere Koenig, MD, MBA, an internist/geriatrician and executive vice president and chief medical officer for Medical Mutual of Ohio, created a dashboard that enabled them to look at who had been admitted with COVID-19 or potential COVID-19 and who needed high acuity care.

“Had we had even more data and a way to share them across a continuum, we would have known where open beds were and we could have provided even better care transitions,” Koenig said.

Collaboration has never been more important in health care. Providers need open channels and clear processes for connecting and communicating with each other and with their constituents.

Collaboration within the health care system, with other local hospitals and skilled nursing facilities (SNF), helps to better address hotspots when they appear, prepare for transitions, and provide more seamless transfers.

“COVID-19 made us think about the importance of the patient experience, and ensuring that team members at SNFs have as much time as possible to spend with patients,” said Lori Baker, MSOL, MSW, director of ambulatory care management and senior services/post-acute care at TriHealth in Cincinnati, Ohio. “Collaboration between hospital systems and postacute care systems is integral to providing safer, more compassionate care transitions.”

5. Every business needs a preparedness plan.
It’s easy to say, “We should have been better prepared,” but the more effective response is, “Now we know how to prepare.” An effective preparedness plan covers the staffing, support, and supplies necessary to ensure facilities are equipped to be successful and to execute quickly in crisis. It accounts for all patients, provides a broad view, and includes key administrators, associations, departments of public health, local and county health services, health plans, medical groups, and anyone else who is involved in patient care. It also dictates how these entities work together and align to be effective and efficient.

“Preparedness starts with knowing your patient population and understanding their needs,” said Skelly Wingard, MS, BSN, RN, vice president, continuum of care, for Kaiser Permanente, Mid-Atlantic states.

“Chart-level data help you to identify high-risk patients and the resources they need, and you need an understanding of your partners so you know who has resources to help when you need it,” Wingard said.

“The more data you have and the better you understand them, the better equipped you are to react and intervene when tragedy strikes.”
First Dataset Is Released on Parkinson Disease and COVID-19

The Michael J. Fox Foundation for Parkinson’s Disease Research has released results from the first and largest ever survey of people with Parkinson disease (PD) to identify a number of consequences associated with coronavirus disease 2019 (COVID-19). PD status was a significant predictor of the negative impact of COVID-19 on daily life, regardless of age and race. In this Article, we describe the survey methodology, the research findings, and the next steps for research and action.

The Fox Insight dataset included 51 patients with PD who had a COVID-19 diagnosis. During their active infection, 55% of them reported a worsening of present motor symptoms, such as tremor, slowness, or balance issues, and more than half reported a worsening of nonmotor symptoms such as mood issues, gastrointestinal challenges, pain, and fatigue.

Symptoms related to COVID-19 were generally similar between those with and without PD; those with PD reported pneumonia (n = 4; 7.8%), a need for supplemental oxygen (n = 6; 12.0%), hospitalization (n = 5; 9.8%), admission to the intensive care unit (n = 2; 3.9%), and being placed on a ventilator (n = 1; 1.9%). Comparatively, those with COVID-19 without PD reported those same outcomes in 3 (12%), 2 (7.7%), 2 (7.7%), 1 (3.8%), and 0 (0%) patients, respectively.

Of the total surveyed group, 62% reported having canceled health care appointments, involuntary reductions of required in-home care, or difficulty in obtaining medication. Being nonwhite and having lower income were both found to be independently associated with difficulty in obtaining medicines for PD. Use of telemedicine appointments were reported by 39% of people with PD, but those with lower incomes were found to be less likely to attend appointments through telemedicine.

Overall, 35% of respondents with PD reported issues in completing ≥1 essential daily activity, such as getting food. Many reported that exercise or social activities—cornerstones of their care—needed to be canceled due to these challenges. A portion of patients noted that they took online classes to continue activities, but those of lower income status were less likely to report alternative ways of seeking care. The interruptions to care in combination with self-isolation were associated with worsening of PD-related symptoms.

Phase 3 Study of BAN2401 in Preclinical Alzheimer Disease Is Announced

Eisai and Biogen, in conjunction with the Alzheimer’s Disease Cooperative Study and the Alzheimer’s Disease Clinical Trials Consortium, have launched the Phase 3 trial of BAN2401 in those with preclinical Alzheimer disease (AD). BAN2401, a humanized monoclonal antibody that selectively binds to neutralize and eliminate toxic amyloid-beta (Aβ) protofibrils, are thought to be a causative factor of AD, is currently being studied in a pivotal Phase 3 trial in symptomatic early AD.

The target enrollment of 1,400 patients will be treated with BAN2401 for 216 weeks. A common screening period will be conducted, after which patients will be randomized to 1 of 2 trials: A3 and A45.

“It is hoped that initiating treatment much earlier in the disease process may be advantageous in preventing future cognitive decline. The AHEAD 3-45 trial should provide critically important answers about the optimal time to intervene with anti-amyloid therapy,” said co-principal investigator Reisa A. Sperling, MD, MMSc, director of the Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital in Boston, in a statement.

A45 will enroll cognitively unimpaired participants who have elevated levels of amyloid and will seek to assess BAN2401’s ability to prevent cognitive decline and suppress the progression of brain AD pathology. The primary end point is the change from baseline in the Preclinical Alzheimer Cognitive Composite 5 at 216 weeks. Its secondary end points are changes from baseline in brain amyloid levels as measured by amyloid PET, as well as brain tau levels as measured by tau PET and Cognitive Function Index.

The A3 trial will include those without cognitive impairment who have intermediate amyloid levels and are at high risk for further Aβ accumulation. The primary end point is the change from baseline in brain amyloid levels as measured by amyloid PET, while the secondary end point is the change from baseline in brain tau levels as measured by tau PET.

Both A3 and A45 will include exploratory end points in a subset consisting of additional clinical assessment scales, imaging, blood biomarkers, and cerebrospinal fluid. An amyloid, tau, and neurodegeneration biomarker panel of imaging and biofluid markers will be used for the assessment of effects on the progression of pathophysiologic changes. Those include Aβ 1-42, Aβ 1-40, t-tau, p-tau, neurogranin, and neurofilament light chain.

Ticagrelor Plus Aspirin Reduces Rate of Stroke or Death

Treatment with ticagrelor (Brilinta; AstraZeneca) lowers the risk of stroke or death among patients with mild-to-moderate acute noncardioembolic ischemic stroke (AIS) or transient ischemic attack (TIA) not undergoing intravenous or endovascular thrombosis, according to results of the THALES (NCT03354429) trial.

Patients administered 90-mg ticagrelor twice daily with aspirin (n = 5,523) saw a 17% reduction in the rate of the primary composite end point of stroke and death (HR, 0.83; 95% CI, 0.71-0.96; P = .02) compared with aspirin alone (n = 5,493).

The primary outcome, a composite of stroke or death within 30 days, occurred in 303 patients (5.5%) in the ticagrelor/aspirin group and in 362 patients (6.6%) in the aspirin group. Ischemic stroke occurred in 276 patients (5.0%) in the ticagrelor/aspirin group and in 345 patients (6.3%) in the aspirin group (HR, 0.79; 95% CI, 0.68-0.93; P = .004).

The secondary outcome of overall disability, measured as >1 on the modified Rankin Scale (mRS), occurred in 23.8% of patients in the ticagrelor/aspirin group and in 24.1% of patients in the aspirin group (OR, 0.98; 95% CI, 0.89-1.07; P = .61). Disabling stroke, measured as mRS score more than 2, occurred in 2.7% of patients in the ticagrelor/aspirin group and in 3.5% of the patients in the aspirin group.
Severe bleeding, the primary safety end point of the study, occurred in 28 patients (0.5%) in the ticagrelor/aspirin group and in 7 patients (0.1%) in the aspirin group (HR, 3.99; 95% CI, 1.74-9.14; P = .001). A composite outcome event of intracranial hemorrhage or fatal bleeding occurred in 22 (0.4%) and 6 (0.1%) patients in the ticagrelor/aspirin and aspirin groups, respectively.

Results of the trial come less than a week after AstraZeneca announced that the FDA had accepted its supplemental new drug application and granted priority review designation for ticagrelor for the reduction of subsequent stroke in patients who experienced an AIS or TIA.2 The Prescription Drug User Fee Act date for ticagrelor is scheduled for the fourth quarter of 2020.

REFERENCES

Early-Life Cognitive Enrichment Leads to Better Late-Life Cognitive Health

Data from the Rush Memory and Aging Project, a clinical-pathological community-based cohort study, suggest that early-life cognitive enrichment (ELCE) is associated with better late-life cognitive health, in part through an association with fewer Alzheimer disease (AD) pathological changes.1

The study, conducted by Shahram Oveisgharan, MD, an assistant professor at the Rush Alzheimer’s Disease Center of Rush University Medical Center in Chicago, and colleagues showed that a higher level of ELCE was associated with less cognitive decline (mean, −0.13 [standard deviation (SD), 0.19] units per year; range, −1.74 to 0.85).

After using a linear regression model that controlled for age at death, sex, and educational level, a higher level of ELCE was associated with a lower global AD pathology score (estimate, −0.057; standard error (SE), 0.022; P = .04) compared with patients with lower levels of ELCE.

AD pathology score persisted (estimate in the model including vascular risk factors, −0.052 [SE, 0.022; P = .02]; estimate in the model including vascular diseases, −0.052 [SE, 0.022; P = .02]; estimate in the model including socioeconomic status, −0.089 [SE, 0.035; P = .01]; estimate in the model including cognitive activity, −0.060 [SE, 0.022; P = .007]).

Multiple cases of data from this project and others have confirmed hypotheses about the benefits from early-life cognitive enrichment and healthy lifestyle habits.

A breakthrough study conducted by Richard Isaacson, MD, director of the Alzheimer’s Prevention Clinic, Weill Cornell Memory Disorders Program at New York’s Weill Cornell Medical College/New York–Presbyterian Hospital, and colleagues, published in October 2019, also suggested that adherence to individually tailored interventions, including behavioral, dietary, pharmacologic, educational, and other recommendations, can have a positive impact on cognition and reduce risk in patients across the clinical spectrum who have a family history of Alzheimer disease.2

Results of the study placed extra emphasis on the importance of early intervention and good adherence, with data demonstrating that higher compliance in patients across the spectrum, from cognitively normal to those with mild cognitive impairment due to AD, resulted in significantly better improvement in cognition than seen in natural history cohorts.

REFERENCES

TICAGRELOR SHINES IN PHASE 3 THALES TRIAL

Naeem Khan, MD, vice president of AstraZeneca’s Cardiovascular and Metabolic Diseases Portfolio, discusses the THALES trial and why ticagrelor has a unique path compared with other stroke treatments.

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"We’re still in the midst of a different and persevering pandemic, and I’m not talking about COVID-19. I’m talking about Parkinson disease and neurodegenerative disorders in general. If we do not find a cure, there will be more people dying of these disorders in 20 to 30 years than all of cancer.”

—Hubert Fernandez, MD
Director, Center for Neurological Restoration, Cleveland Clinic

[W]e’re going to learn a ton about drug development and how the FDA views these things by what happens to aducanumab.”

—Jeffrey Cummings, MD, ScD
Director emeritus, Lou Ruvo Center for Brain Health, Cleveland Clinic
Vice chair, Department of Brain Health, University of Nevada, Las Vegas
I’m hopeful that this immediate transformation of care in the outpatient medicine setting will let our residents reach even more underserved patients—people with physical or cognitive disabilities who ordinarily might have had their office visits cancelled or postponed—and I’m hoping that that part of medical access for our patients with brain disorders enhances their learning in the long run.”

—Matthew Robbins, MD
Director, Neurology Residency Program
Weill Cornell Medicine

**THE ROLE OF ASTROCYTES AND MICROGLIA IN CELL DEATH**
Eyiyeemi Damisah, MD, assistant professor of neurosurgery at Yale School of Medicine, speaks about her research to better understand the process of cell death and corpse removal in the brain, and how it may play a role in combating neurodegeneration.

**THE FUTURE LANDSCAPE IN NMOSD**
Bruce Cree, MD, PhD, MAS, clinical research director at University of California, San Francisco (UCSF) Multiple Sclerosis Center and professor of clinical neurology, UCSF Weill Institute for Neurosciences, discusses current treatment options for NMOSD and what the future may hold.

**MASCULINITY AND MULTIPLE SCLEROSIS**
Bryan Davis, PsyD, MS, clinical health psychology fellow at the Mellen Center for Multiple Sclerosis Treatment and Research at Cleveland Clinic, provides his takeaways from a recent research project that set out to explore the effects of gender norms and masculinity on men with multiple sclerosis.

**EXPLORING THE LINK BETWEEN STROKE AND COVID-19**
Shadi Yaghi, MD, director of clinical vascular neurology research at NYU Langone Health and director of vascular neurology at NYU Langone Hospital-Brooklyn, offers some perspective on the challenges of understanding the relationship between COVID-19 and stroke.

**SEQUENCING SNPS IN HUNTINGTON DISEASE**
Daniel Claassen, MD, MS, associate professor of neurology, cognitive and behavioral neurology, and movement disorders at Vanderbilt University Medical Center, discusses the feasibility of clinical trials using therapies that target single nucleotide polymorphisms in patients with Huntington disease.

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INDICATION

MAYZENT® (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindications
- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Infections: MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected, MAYZENT should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization
FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN RMS¹

STAY AHEAD OF PROGRESSION WITH MAYZENT® (siponimod)

MAYZENT IS THE FIRST AND ONLY oral DMT studied and proven to delay disability progression in a more progressed patient population in RMS (mean EDSS score of 5.4)¹³

THE DUAL MOA OF MAYZENT targets S1P₁,₅—2 key receptors thought to play a role in RMS inflammation and neurodegeneration. MAYZENT works in the periphery to limit active lymphocytes from leaving the lymph nodes, which may reduce lymphocyte migration into the CNS¹⁴-⁷

DEMONSTRATED SAFETY PROFILE in the largest trial designed for this more progressed patient population in RMS¹³,⁸

The mechanism by which siponimod exerts therapeutic effects on MS is unknown.¹

CNS=central nervous system; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; MOA=mechanism of action; RMS=relapsing multiple sclerosis.

LEARN ABOUT THE POTENTIAL SIGNS OF PROGRESSION

IMPORTANT SAFETY INFORMATION (CONT)

Infections (cont): is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

Caution should be used when combining treatment (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
MAYZENT® (siponimod) tablets, for oral use

Please see additional Important Safety Information on the previous pages and Brief Summary of full Prescribing Information on adjacent pages.


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MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

MAYZENT is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

4 CONTRAINDICATIONS

MAYZENT is contraindicated in patients who have:

- A CYP3A4 3A3 genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5) in the full prescribing information].
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, uncompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless the patient has a functioning pacemaker [see Warnings and Precautions (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of infections

MAYZENT causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections, some serious in nature [see Clinical Pharmacology (12.2) in the full prescribing information]. Life-threatening and rare fatal infections have occurred in association with MAYZENT.

In Study 1 [see Clinical Studies (14) in the full prescribing information], the overall rate of infections was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent complete blood count (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period [see Warnings and Precautions (5.1)].

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Cryptococcal Infections

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine-1-phosphate (SIP) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections

Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the overall rate of Herpes zoster infections was 4.6% in MAYZENT-treated patients compared to 3.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT [see Vaccinations below].

Progressive Multifocal Leuкоencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe neurological 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.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with a SIP receptor modulator and multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). 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 MAYZENT should be suspended until PML has been excluded.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy [see Drug Interactions (7.1)].

Vaccinations

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT, following which initiation of treatment with MAYZENT should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment [see Drug Interactions (7.1)].

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema

Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.3 Bradycardia and Atioventricular Conduction Delays

Since initiation of MAYZENT treatment results in a transient decrease in heart rate and atioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of MAYZENT [see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2) in the full prescribing information].

MAYZENT was not studied in patients who had:

- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, or uncompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest, Mobitz type II AV block, symptomatic bradycardia, sick sinus syndrome, Mobitz type I second degree AV-block or higher grade AV-block (either history or observed at screening), unless the patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class la or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]

Reduction in Heart Rate

After the first titration dose of MAYZENT, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3-4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days, with maximal decrease from Day 1-baseline reached on Day 5-6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5-6 bpm. Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention [see Adverse Reactions (6.1)]. Heart rates below 40 bpm were rarely observed.

Atioventricular Conduction Delays

Initiation of MAYZENT treatment has been associated with transient atioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested in most of the cases as first-degree AV block (prolonged PR interval on ECG), which occurred in 5.1% of MAYZENT-treated patients and 1.9% of patients receiving placebo in Study 1. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at the time of treatment initiation with MAYZENT in less than 1.7% of patients in clinical trials. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, rarely required treatment with atropine, and did not require discontinuation of MAYZENT treatment.

If treatment with MAYZENT is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec)
- In patients with arrhythmias requiring treatment with Class la or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]
- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block [see Contraindications (4)]

Treatment-Initiation Recommendations

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects [see Dosage and Administration (2.2, 2.3) in the full prescribing information].
- In patients with sinus bradycardia (HR less than 55 bpm), first- or second-grade (Mobitz type I) AV block, or a history of myocardial infarction or heart failure with onset > 6 months prior to initiation, ECG testing and first-dose monitoring is recommended [see Dosage and Administration (2.1, 2.4) in the full prescribing information].
- Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.
Use of MAYZENT in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

Experience with MAYZENT is limited in patients receiving concurrent therapy with drugs that decrease heart-rate (e.g., beta-blockers, calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate, such as ivabradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.

For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing MAYZENT treatment. If the resting heart rate is greater than 50 bpm under chronic beta-blocker treatment, MAYZENT may be introduced. If resting heart rate is less than or equal to 50 bpm, beta-blocker treatment should be interrupted until the baseline heart-rate is greater than 50 bpm. Treatment with MAYZENT can then be initiated and treatment with a beta-blocker can be reinstituted after MAYZENT has been up-titrated to the target maintenance dosage [see Drug Interactions (7.3)].

For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate [see Dosage and Administration (2.4) in the full prescribing information and Drug Interactions (7.2)].

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

If a titration dose is missed or if 4 or more consecutive daily doses are missed during maintenance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommendations [see Dosage and Administration (2.2, 2.3) in the full prescribing information].

5.4 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MAYZENT-treated patients as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV1 from baseline to placebo was 88 mL (95% confidence interval (CI): 139, 37) at 2 years. The mean difference between MAYZENT-treated patients and patients receiving placebo in percent predicted FEV1, at 2 years was 2.8% (95% CI: -4.5, -1.0). There is insufficient information to determine the reversibility of the decrease in FEV1, after drug discontinuation. In Study 1, five patients discontinued MAYZENT because of decreased in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV1 were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

5.5 Liver Injury

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of MAYZENT therapy.

In Study 1, elevations in transaminases and bilirubin were observed in 10.1% of MAYZENT-treated patients compared to 3.7% of patients receiving placebo, mainly because of transaminase [alanineaminotransferase/aspartate aminotransferase/gamma-glutamyltransferase (ALT/AST/GGT)] elevations.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of MAYZENT. In clinical trials, MAYZENT was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should have liver enzymes checked. MAYZENT should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

5.6 Increased Blood Pressure

In Study 1, MAYZENT-treated patients had an average increase over placebo of approximately 3 mmHg in systolic pressure and 1.2 mmHg in diastolic pressure, which was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertension was reported as an adverse reaction in 12.5% of MAYZENT-treated patients and in 9.2% of patients receiving placebo. Blood pressure should be monitored during treatment with MAYZENT and managed appropriately.

5.7 Fetal Risk

Based on animal studies, MAYZENT may cause fetal harm [see Use in Specific Populations (8.1)]. Because it takes approximately 10 days to eliminate MAYZENT from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT treatment.

5.8 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1-phosphate (SIP) receptor modulator. Such events have not been reported for MAYZENT-treated patients in the development program. However, should a MAYZENT-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider a MRI. 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, MAYZENT should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

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, when initiating MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended [see Drug Interactions (7.1)].

5.10 Severe Increase in Disability After Stopping MAYZENT

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a SIP receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping MAYZENT

After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy [see Clinical Pharmacology (12.2) in the full prescribing information]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 3-4 weeks after the last dose of MAYZENT [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Infections [see Warnings and Precautions (5.1)]
- Macular Edema [see Warnings and Precautions (5.2)]
- Bradyarrhythmia and Atrioventricular (AV) Conduction Delays [see Warnings and Precautions (5.3)]
- Respiratory Effects [see Warnings and Precautions (5.4)]
- Liver Injury [see Warnings and Precautions (5.5)]
- Increased Blood Pressure [see Warnings and Precautions (5.6)]
- Fetal Risk [see Warnings and Precautions (5.7)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressives [see Warnings and Precautions (5.9)]

Severe Increase in Disability After Stopping MAYZENT [see Warnings and Precautions (5.10)]

Immune System Effects After Stopping MAYZENT [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 [see Clinical Studies (14) in the full prescribing information] and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.

<table>
<thead>
<tr>
<th>Adverse Reaction Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)</th>
<th>MAYZENT 2 mg (N = 1099)</th>
<th>Placebo (N = 546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Transaminase increaseda</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Falls</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Terms were combined as follows:

- headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
- hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
- alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
- edema peripheral, joint swelling, fluid retention, swelling face.
- bradycardia, sinus bradycardia, heart rate decreased.

In 4% of patients, patients experienced limb discomfort.

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), asthenia, and pulmonary function test decreased [see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)].
Seizures
In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Respiratory Effects
Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) were observed in patients treated with MAYZENT [see Warnings and Precautions (5.4)].

Vascular Events
Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Malignancies
Malignancies such as malignant melanoma in situ and seminoma were reported in MAYZENT-treated patients in Study 1. An increased risk of cutaneous malignancies has been reported in association with another S1P modulator.

7 DRUG INTERACTIONS
7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies
MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration [see Warnings and Precautions (5.1)].

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects [see Warnings and Precautions (5.1)].

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended.

MAYZENT can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate
MAYZENT has not been studied in patients taking QT prolonging drugs.

Class la (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of torsades de Pointes in patients with bradycardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazen), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) [see Warnings and Precautions (5.3) and Drug Interactions (7.3)]. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers
Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT [see Warnings and Precautions (5.3)]. Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT [see Clinical Pharmacology (12.2) in the full prescribing information].

7.4 Vaccination
During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination [see Warnings and Precautions (5.1)].

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT [see Warnings and Precautions (5.1)].

7.5 CYP2C9 and CYP3A4 Inhibitors
Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluorconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYP2C9 and CYP3A4 Inducers
Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, elafinicity) or strong CYP3A4 inducers is not recommended for patients with CYP2D1*1/*3 and 2/*2 genotype [see Clinical Pharmacology (12.2) in the full prescribing information].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman [see Data]. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified.

Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 2 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolethality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less than that in humans at the RHD.

When siponimod (0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturation were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m² basis.

8.2 Lactation
Risk Summary
There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Contraception
Females
Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT [see Use in Specific Populations (8.1)]. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period [see Warnings and Precautions (5.7)].

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYP2C9 Genotype
Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosing adjustment is recommended in patients with CYP2C9*1/*1 or *2/*2 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5) in the full prescribing information].

10 OVERDOSAGE
In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed [see Warnings and Precautions (5.2, 5.6) and Clinical Pharmacology (12.2) in the full prescribing information].

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

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Combination OnabotulinumtoxinA and CGRP Treatment Safe, Effective in Migraine

The addition of an anti-CGRP agent may help further reduce monthly headache days without significantly adding to the adverse effect burden.

By Matt Hoffman

NEW DATA FROM A retrospective chart review of patients with chronic migraine receiving treatment with onabotulinumtoxinA who have been prescribed a calcitonin gene-related peptide (CGRP) monoclonal antibody suggest that the new class of medicines are safe and effective for those who require additional preventive treatment.1

Ultimately, in a cohort of 153 patients treated with onabotulinumtoxinA, 66 continued to have 14.3 monthly headache days (MHDs) despite significant reductions from baseline headache days prior to treatment with onabotulinumtoxinA (baseline, 25.3 days; reduction, 10.9 days [43%; \( P < .0001 \)). The add-on of a CGRP therapy was associated with an additional decrease of 5.6 days, equating to an additional 22.3% reduction (95% CI, 4.5-6.7; \( P < .0001 \)) in MHDs.

Of the 153-patient study population, 88 (58%) were treated with erenumab (Aimovig; Novartis), 51 (33%) were treated with galcanezumab (Emgality; Eli Lilly), and 14 (9%) were treated with fremanezumab (Ajovy; Teva). The data were presented by Fred Cohen, MD, internal medicine resident physician in the Department of Medicine at Montefiore Health System, at the American Headache Society (AHS) Virtual Annual Scientific Meeting on June 13, 2020.

“We have shown that CGRP monoclonal antibodies are an effective and well-tolerated treatment option for patients with chronic migraine who are undergoing treatment with onabotulinumtoxinA but require additional preventive therapy,” Cohen said in the presentation. “The addition of a CGRP monoclonal antibody provided statistically significant [fewer] MHDs. However, this was a retrospective chart review, which is hindered by elements such as recall bias; therefore, future prospective studies are warranted for higher-quality data.”

In total, those treated additionally with CGRP medicines experienced an overall reduction of 16.6 MHDs (95% CI, 13.8-19.3; \( P < .0001 \)) from baseline, prior to onabotulinumtoxinA treatment. In total, 13 patients (8.5%) reported adverse effects associated with the CGRP medications that included constipation, injection site reaction, and fatigue.

“The data for efficacy outcomes and safety profile when adding a CGRP monoclonal antibody to patients who are already receiving onabotulinumtoxinA are limited,” Cohen explained. “This is, in part, due to the fact that during the clinical trials for CGRP monoclonal antibodies, patients treated with onabotulinumtoxinA were excluded.”

When exploring the reductions with each CGRP agent, the observations were similar. The erenumab, galcanezumab, and fremanezumab groups experienced baseline MHDs of 26.1, 24.9, and 26.2 days, respectively, and then reductions of 11.3 (MHDs, 14.8), 10.3 (MHDs, 14.6), and 11.7 days (MHDs, 14.5) with onabotulinumtoxinA. After the introduction of erenumab, those on onabotulinumtoxinA experienced a further reduction of 5.5 days (MHDs, 9.3), while those introduced to galcanezumab and to fremanezumab experienced reductions of 5.3 days (MHDs, 9.3) and 8.7 days (MHDs, 5.8), respectively.
UBROGEPANT EFFECTIVE FOR PATIENTS WITH MIGRAINE WITH INSUFFICIENT TRiptAN RESPONSE

The recently approved agent was associated with lower rates of functional disability and better overall satisfaction with treatment.

By Matt Hoffman

THOSE WITH MIGRAINE WHO experience an insufficient response to triptans who are treated with ubrogepant (Ubrely; Allergan) reported lower rates of functional disability and better overall satisfaction with treatment compared with those randomized to placebo.1

All told, 2 hours post dose, those treated with ubrogepant reported higher odds of achieving function normally from 2 to 8 hours after the initial dose, as measured by the Patient Global Impression of Change (OR, 1.84; 95% CI, 1.19-2.83; P = .006). Additionally, a higher proportion of ubrogepant-treated patients indicated that migraine was much better or very much better 2 hours post initial dose, as measured by the Patient Global Impression of Change (OR, 2.00; 95% CI, 1.22-3.29; P = .006), and there were no differences in treatment effects based on historical triptan experiences.

The data, pulled from the ACHIEVE I (NCT02828020) and II (NCT02867709) trials, were presented by Richard B. Lipton, MD, director, Montefiore Headache Center, and professor of neurology, Albert Einstein College of Medicine, at the American Headache Society Virtual Annual Scientific Meeting on June 13, 2020. This dataset included a total of 1799 participants (placebo: n = 912; ubrogepant 50 mg: n = 887).

“We’ve seen that a significantly higher proportion of triptan-insufficient responders treated with ubrogepant reported being able to function normally from 2 to 8 hours after the initial dose, in comparison with placebo-treated patients,” Lipton said in his presentation. “We’ve seen that more triptan-insufficient responders who took ubrogepant were satisfied with the treatment at 2 and 24 hours and indicated improvement in their migraine at 2 hours versus placebo.”

At baseline, 38% of participants (n = 682) were categorized as triptan responders, 25% (n = 451) as triptan-insufficient responders, and 37% (n = 666) as triptan naïve. Those who were deemed insufficient responders made up 24.5% (n = 223) of the placebo group and 25.7% (n = 228) of the ubrogepant group. The subgroups of insufficient responders in each group included those with insufficient efficacy (placebo: 78% [n = 174]; ubrogepant: 81.1% [n = 185]), poor tolerability (placebo: 17% [n = 38]; ubrogepant: 16.2% [n = 37]), and contraindications (placebo: 3.1% [n = 7]; ubrogepant: 2.2% [n = 5]).

Lipton noted that the oral calcitonin gene-related peptide (CGRP) antagonist was deemed both safe and well tolerated with no new safety signals.

“In terms of safety, the incidence of treatment-emergent adverse events [AEs] and treatment-related AEs did not differ appreciably across historical triptan-use subgroups. Among triptan-insufficient responders, 12.1% of participants in the placebo group and 15.4% of participants in the ubrogepant group reported treatment-emergent AEs within 48 hours. No serious AEs were reported in any subgroup,” he explained.

Patients in the 2 groups were compared based on Functional Disability Scale scores at 2, 4, and 8 hours post dose. At those respective time points, the proportions of insufficient triptan responders in the ubrogepant group who were able to function normally were 38%, 56%, and 73%. In comparison, for those same time points, 29%, 40%, and 57% of the placebo group reported normal function (P < .05 for all).

For the subgroup of patients with insufficient efficacy with triptans, the results were similar, although significant only at the
Youth With Migraine Improve After Preventive Treatment Regardless of Therapy Continuation

Results from the CHAMP trial of adolescents and children with migraine add to the active and ongoing discussion about the use of preventives in this population.

By Matt Hoffman

DATA FROM A SURVEY of the 3-year CHAMP trial presented at the American Headache Society (AHS) Virtual Annual Scientific Meeting on June 13, 2020, suggest that children and adolescents with migraine who are treated with pill-based preventive therapy can maintain improvements in headache days and disability, and they can continue to improve without ongoing use of preventives.1

In total, aside from the 12-month mark when the placebo group had better headache reduction compared with the topiramate group (difference, –2.58 days; 95% CI, –5.35 to 0.35; P = .03), all other comparisons between those groups and an amitriptyline-treated group showed no differences in the 3 time points assessed (amitriptyline vs placebo: 12, 24, 36 months; amitriptyline vs topiramate: 12, 24, 36 months; topiramate vs placebo: 24, 36 months).

“These novel findings have direct implications for practice guidelines. In fact, in 2019, the latest guidelines were published in Neurology, specifically requesting data on long-term follow-up,” study author Scott Powers, PhD, ABPP, professor of pediatrics, Cincinnati Children’s Research Foundation Endowed Chair, scientific director of Clinical Research and Trials, co-director of the Headache Center, and director of the Center for Child Behavior and Nutrition Research and Training at Cincinnati Children’s Hospital and University of Cincinnati College of Medicine, said in his presentation, citing the joint AHS–American Academy of Neurology guidelines published last August.2,3

“For clinicians, these data strongly suggest that, if you use a prevention medication or pill-taking approach, it can be stopped with realistic and informed expectations for continued good functioning over time,” Powers added.

An initial posttrial survey, intended to examine headache days and disability at 3, 6, 12, 18, 24, and 36 months post CHAMP, was completed by 203 participants with high retention (6 months: 92%; 12 months: 88%; 18 months: 80%; 24 months: 81%; 36 months: 73%). The respondents averaged 11 monthly headache days (MHDs) at trial baseline and had an average Pediatric Migraine Disability Assessment (PedMIDAS) score of 41. Post CHAMP, MHDs were reduced to 5 and PedMIDAS scores were lowered to 18.

All told, amitriptyline decreased MHDs, on average, by 3.98 days (95% CI, 2.46-5.49; P <.001), while topiramate reduced them by 2.26 days (85% CI, 0.63-3.89; P <.0069), and placebo reduced them by 4.84 days (95% CI, 2.81-6.87; P <.0001).

For PedMIDAS scores, all 3 treatment arms showed significant improvement from trial baseline to the 12-month survey time point, with no differences found among groups. Similarly, there was also no interaction between treatment group and responder status.

Notably, at each survey time point, only 20% to 28% of respondents reported current preventive medication use. No statistically significant differences of this variable among the treatment groups at any of the 12-, 24-, and 36-month time points were identified.

“We know that most youth in the CHAMP trial improved, and now we know that those improvements were maintained up to 3 years,” Powers said in his presentation. “We also know, consistent with the CHAMP trial, there were no differences that emerged favoring either medication, and up to 88% did not continue to take a prescription prevention medicine for migraine. This is important to communicate to families.”

Powers and colleagues concluded, saying that, “These results imply that we should expect youth to improve and that they continue to do well up to 3 years after that improvement. Continuation of a pill-based therapy is generally not indicated based on these results.”
Treating Eye Pain and Photophobia in Migraine

By Alicia Bigica

MORE AND MORE, clinical end points included in migraine treatment trials account for patients’ “most bothersome symptom.” On that list of symptoms is typically photophobia.

Despite the common nature of this complaint, willingness to address it head on as part of the migraine treatment process is often overlooked. Kathleen Digre, MD, distinguished professor of neurology and ophthalmology at the John A. Moran Eye Center and chief of the Division of Headache and Neuro-ophthalmology at the University of Utah in Salt Lake City, hears this often from patients, many of whom have seen multiple neurologists and ophthalmologists, yet their eye complaints have not been adequately addressed.

Following her lecture at the 2020 American Headache Society (AHS) Virtual Annual Scientific Meeting, Digre, who is also a past president of the AHS, shared her tips for a thorough exam with NeurologyLive® and what hurdles still stand in the way of improved care for these patients.

Q: Will you share your steps for a thorough exam and diagnosis of patients presenting with eye pain and/or photophobia?

First take a careful history, asking about underlying migraine, head injuries, chronic pain conditions, and other things that could cause this to occur. Then on the examination, I look for findings that could point me to a secondary cause like Horner syndrome or papilledema, or a pupillary defect. Those are usually eye complaints and that person probably should see an ophthalmologist who can look at the retina and macula.

The next step is to figure out whether the cornea or dry eyes are playing a role in the light sensitivity or in the eye pain. If a substantial part of the pain and light sensitivity goes away with a drop of proparacaine, that means corneal nerves are perpetuating or making the light sensitivity and the eye pain worse. Next is a Schirmer’s test, which involves a little piece of litmus paper that tells you whether there’s dryness to the eye and if a tear production problem could be occurring. If it’s that, then you’ve got something else you can treat to get rid of the light sensitivity, etc. I also look for blepharospasm, which is another neurologic condition with frequent blinking. It has 2 forms: the frequent blinking or the inordinate closure of the eyes. If they have migraine, it’s playing a role in this; whether it’s playing a primary role or a secondary role doesn’t matter. People who have migraine are more prone to photophobia and they are prone to central sensitization, especially if they have chronic migraine, which can keep the pain going.

Q: How much does our current understanding of the pathophysiology of this pain factor into it not being diagnosed or treated correctly?

When we found out about these melanopsin cells or intrinsically photosensitive retinal ganglion cells, that really changed the landscape for me personally, because I would have patients who were legally blind and yet they were so photophobic. These melanopsin cells are phylogenetically very, very old cells that live in our retina and sense light. They anatomically connect to the pain center, the trigeminal pathway.

Researchers have studied lab mice who are born actually blind for about 7 days; during that time, they shine light on them and they squeak. The mice are anxious and their brains show that their limbic system is impacted. When studying melanopsin knockout mice, [those mice] don’t have this same squeaking going on, so we know that melanopsin is playing a role in this. How do we control that pathway? That we don’t know. There are some big knowledge gaps of what treatments we could use that would help to bring that down.

Q: Would you like the neurology and ophthalmology communities to know anything else about these symptoms?

Every ophthalmologist needs to know about migraine and realize that migraine could participate in their patients’ eye pain and light sensitivity. The neurologist may be uncomfortable about the eye pain or photophobia, but they can partner with an ophthalmologist and then start treating the underlying migraine component. It’s important to not forget depression and anxiety; migraine doesn’t usually kill people, but depression can, so it’s really important that we recognize it and take it seriously. I think one of the most powerful things [a clinician] can do is say to a patient, “There’s an anatomic basis for this and a physiologic basis for this. You’re not making this up. It’s not all in your head.” Let’s take care of the eye component, the migraine component, the pain component, and the depression/anxiety component, and by doing that we can do a better job of taking care of these people.
WHEN YOUR PATIENTS WITH LGS OR DRAVET SYNDROME NEED A DIFFERENT APPROACH

It’s time to explore a novel path

The first and only FDA-approved cannabidiol¹

A first-in-class antiepileptic drug (AED) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.
Studied in the largest controlled pivotal clinical trial program in LGS and Dravet syndrome to date (N=516)\(^2-4\)

IMPORTANT SAFETY INFORMATION (CONT’D)

WARNINGS & PRECAUTIONS

Hepatocellular Injury:
EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury.

Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Adverse Reactions:
The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

Pregnancy:
EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

Drug Interactions:
Moderate or strong inhibitors or inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam) or others. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

Drug Abuse:
EPIDIOLEX is a Schedule V controlled substance and has a low potential for abuse.

Please refer to the EPIDIOLEX full Prescribing Information for additional important information.

References:
EPIDIOLEX® (cannabidiol) oral solution, Rx only

INDICATIONS AND USAGE - EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

CONTRAINDICATIONS - EPIDIOLEX is contraindicated in patients with a history of hypersensitivity to cannabidiol or any of the ingredients in the product.[see Description and Warnings and Precautions in full PI].

WARNINGS AND PRECAUTIONS

Hepatotoxicity Injury - EPIDIOLEX causes dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). In controlled studies for LGS and DS, the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 14% in EPIDIOLEX-treated patients compared with 1% in patients on placebo. Less than 1% of EPIDIOLEX-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking EPIDIOLEX. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX or reduction of EPIDIOLEX and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with EPIDIOLEX without dose reduction.

Risk Factors for Transaminase Elevation:

Concomitant Valproate and Clobazam - The majority of ALT elevations occurred in patients taking concomitant valproate. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate [see Drug Interactions in full PI]. In EPIDIOLEX-treated patients, the incidence of ALT elevations greater than 3 times the ULN was 30% in patients taking both concomitant valproate and clobazam, 21% in patients taking concomitant valproate (without clobazam), 4% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug. Consider discontinuation or dose adjustment of valproate or clobazam if liver enzyme elevations occur.

Dose - Transaminase elevations are dose-related. Overall, ALT elevations greater than 3 times the ULN were reported in 17% of patients taking EPIDIOLEX 20 mg/kg/day compared with 1% in patients taking EPIDIOLEX 10 mg/kg/day.

Baseline Transaminase Elevations - Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking EPIDIOLEX. In controlled trials (Studies 1, 2, and 3) in patients taking EPIDIOLEX 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 30% when ALT was above the ULN at baseline, compared to 12% when ALT was within the normal range at baseline. No patients taking EPIDIOLEX 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 2% of patients in whom ALT was within the normal range at baseline.

Monitoring: In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, accompanied by elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of EPIDIOLEX treatment. Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in EPIDIOLEX dosage and addition of or changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX, as appropriate. Discontinue EPIDIOLEX in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Consider dosage adjustment of any co-administered medication that is known to affect the liver (e.g., valproate and clobazam).

Somnolence and Sedation - EPIDIOLEX can cause somnolence and sedation. In controlled studies for LGS and DS, the incidence of somnolence and sedation (including lethargy) was 32% in EPIDIOLEX-treated patients, compared with 11% in patients on placebo and was dose-related (34% of patients taking EPIDIOLEX 20 mg/kg/day, with 27% in patients taking EPIDIOLEX 10 mg/kg/day). The rate was higher in patients on concomitant clobazam (46% in EPIDIOLEX-treated patients taking clobazam compared with 16% in EPIDIOLEX-treated patients not on clobazam). In general, these effects were more common early in treatment and may diminish with continued treatment. Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of EPIDIOLEX. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation - Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal behavior or behavior that involves patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thoughts or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed [see Warnings and Precautions in full PI for absolute and relative risk by indication for all evaluated AEDs]. The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of the suicidal thoughts or behaviors with the risk of the untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Hypersensitivity Reactions - EPIDIOLEX can cause hypersensitivity reactions. One subject in the EPIDIOLEX clinical trials had pruritus, erythema, and angioedema requiring treatment with antihistamines. Patients with known or suspected hypersensitivity to any ingredients of EPIDIOLEX were excluded from the clinical trials. If a patient develops hypersensitivity reactions after treatment with EPIDIOLEX, the drug should be discontinued. EPIDIOLEX is contraindicated in patients with a prior hypersensitivity reaction to cannabidiol or any of the ingredients in the product, which includes sesame seed oil [see Description in full PI].

Withdrawal of Antiepileptic Drugs (AEDs) - As with most antiepileptic drugs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus [see Dosage and Administration and Clinical Studies in full PI]. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere [see Warnings and Precautions in full PI].

- Hepatocellular Injury
- Somnolence and Sedation
- Suicidal Behavior and Ideation
- Hypersensitivity Reactions
- Withdrawal of Antiepileptic Drugs

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In controlled and uncontrolled trials in patients with LGS and DS, 689 patients were treated with EPIDIOLEX, including 533 patients treated for more than 6 months, and 391 patients treated for more than 1 year. In an expanded access program and other compassionate use programs, 161 patients with DS and LGS were treated with EPIDIOLEX, including 109 patients treated for more than 6 months, 91 patients treated for more than 1 year, and 50 patients treated for more than 2 years. In placebo-controlled trials of patients with LGS or DS (includes Studies 1, 2, 3, and a Phase 2 controlled trial), 323 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in these trials was up to 14 weeks. Approximately 46% of patients were female, 83% were Caucasian, and the mean age was 14 years (range 2 to 48 years). All patients were taking other AEDs. In controlled trials, the rate of discontinuation as a result of any adverse reaction was 2.7% for patients taking EPIDIOLEX 10 mg/kg/day, 11.8% for patients taking EPIDIOLEX 20 mg/kg/day, and 1.3% for patients on placebo. The most frequent cause of discontinuations was transaminase elevation. Discontinuation for transaminase elevation occurred in 1.3% of patients taking EPIDIOLEX 10 mg/kg/day, 5.9% in patients taking EPIDIOLEX 20 mg/kg/day, and 0.4% in patients on placebo. Somnolence, sedation, and lethargy led to discontinuation in 3% of patients taking EPIDIOLEX 20 mg/kg/day compared to 0% of patients taking EPIDIOLEX 10 mg/kg/day or on placebo. The most common adverse reactions that occurred in EPIDIOLEX-treated patients (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue; malaise; and asthenia; rash; insomnia; sleep disorder, and poor quality sleep; and infections. The table below lists adverse reactions reported in ≥ 2% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo in the placebo-controlled trials in LGS and DS. Adverse reactions were similar across LGS and DS in pediatric and adult patients.
Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EPIDIOLEX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg/day</td>
<td>20 mg/kg/day</td>
</tr>
<tr>
<td>N=75</td>
<td>N=238</td>
<td>N=227</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hepatic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases elevated</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain, discomfort</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Sedation</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lethargy</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue, malaise, asthenia</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Insomnia, sleep disorder, poor quality sleep</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Irritability, agitation</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Aggression, anger</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Urinary, uri/renal</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, all</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Infection, viral</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Infection, bacterial</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Infection, fungal</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Infection, other</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Hypoesthesia, respiratory failure</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Decreased Weight - EPIDIOLEX can cause weight loss. In the controlled trials of patients with LGS or DS, based on measured weights, 16% of EPIDIOLEX-treated patients had a decrease in weight of ≥5% from their baseline weight, compared to 8% of patients on placebo. The decrease in weight appeared to be dose-related, with 18% of patients on EPIDIOLEX 20 mg/kg/day experiencing a decrease in weight ≥5%, compared to 9% in patients on EPIDIOLEX 10 mg/kg/ day. In some cases, the decreased weight was reported as an adverse event (see Table above).

Hematologic Abnormalities - EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was -0.42 g/dL in EPIDIOLEX-treated patients and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.5% in EPIDIOLEX-treated patients, and -0.4% in patients on placebo. There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients on placebo.

Increased in Creatinine - EPIDIOLEX can cause elevations in serum creatinine. The mechanism has not been determined. In controlled studies in healthy adults and in patients with LGS and DS, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS and DS.

DRUG INTERACTIONS

Effect of Other Drugs on EPIDIOLEX

Moderate or Strong Inhibitors of CYP3A4 or CYP2C19: EPIDIOLEX is metabolized by CYP3A4 and CYP2C19. Therefore, coadministration with a moderate or strong inhibitor of CYP3A4 or CYP2C19 will increase cannabidiol plasma concentrations, which may result in a greater risk of adverse reactions. Consider a reduction in EPIDIOLEX dosage when coadministered with a moderate or strong inhibitor of CYP3A4 or CYP2C19 [see Clinical Pharmacology in full PI].

Strong CYP3A4 or CYP2C19 Inducers: Coadministration with a strong CYP3A4 or CYP2C19 inducer will decrease cannabidiol plasma concentrations, which may lower the efficacy of EPIDIOLEX. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) when coadministered with a strong CYP3A4 or CYP2C19 inducer [see Clinical Pharmacology in full PI].

Effect of EPIDIOLEX on Other Drugs

UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2D6 Substrates: In vitro data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., dupropion, efavirenz), uridine 5’t-diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenobart), and UGT2B7 (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinical interaction with CYP2C9 (e.g., omeprazole, phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP1A2 and CYP2B6, as clinically appropriate [see Clinical Pharmacology in full PI].

Sensitive CYP2C19 Substrates: In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates [see Clinical Pharmacology in full PI]. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

Clobazam: Coadministration of EPIDIOLEX produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19) [see Clinical Pharmacology in full PI]. This may increase the risk of clobazam-related adverse reactions [see Warnings and Precautions in full PI]. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when co-administered with EPIDIOLEX.

Concomitant Use of EPIDIOLEX and Valproate - Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations [see Warnings and Precautions in full PI]. Discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.

CNS Depressants and Alcohol - Concomitant use of EPIDIOLEX with other CNS depressants may increase the risk of sedation and somnolence [see Warnings and Precautions in full PI].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as EPIDIOLEX, during pregnancy. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary: There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabinoid to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weight in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses (see Animal Data in full PI).

Lactation

Risk Summary: There are no data on the presence of cannabinoid or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

Pediatric Use - Safety and effectiveness of EPIDIOLEX for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome have been established in patients 2 years of age and older. Safety and effectiveness of EPIDIOLEX in pediatric patients below 2 years of age have not been established.

Geriatric Use - Clinical trials of EPIDIOLEX in the treatment of LGS and DS did not include any patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology in full PI].

Hepatic Impairment - Because of an increase in exposure to EPIDIOLEX, dosage adjustments are necessary in patients with moderate or severe hepatic impairment [see Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology in full PI]. EPIDIOLEX does not require dose adjustments in patients with mild hepatic impairment.

DRUG ABUSE AND DEPENDENCE - Controlled Substance: EPIDIOLEX is controlled in Schedule V of the Controlled Substances Act.

Abuse - Animal abuse-related studies show that cannabinoid does not produce cannabinoid-like behavioral responses, including generalization to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabinoid also does not produce animal self-administration, suggesting it does not produce rewarding effects. In a human abuse potential study, acute administration of cannabinoid to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses of 750, 1500, and 4500 mg in the fasted state (equivalent respectively to 10, 20, and 60 mg/kg in a 75 kg adult) produced responses on positive subjective measures such as Drug Liking and Take Drug Again that were within the acceptable placebo range. In contrast, 10 and 30 mg of drominab (synthetic THC) and 2 mg alprazolam produced large increases on positive subjective measures compared to placebo that were statistically significantly greater than those produced by cannabinoid. In other Phase 1 clinical studies conducted with cannabinoid, there were no reports of abuse-related adverse events.

Dependence - In a human physical dependence study, administration of cannabinoid 1500 mg/ day (750 mg twice daily) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning three days after drug discontinuation. This suggests that cannabinoid likely does not produce physical dependence.

Please see the full PI for Patient Counseling Information

See full Prescribing Information at www.EPIDIOLEX.com.

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Early Intervention in SMA: How Access to Therapy Will Alter Disease Management As We Know It

Efforts to cut through regulatory red tape will help ensure earlier access to potentially lifesaving treatments.

By Kenneth Bender, PharmD, MA

THREE DISEASE-MODIFYING TREATMENTS for spinal muscular atrophy (SMA) that have been approved all have different mechanisms of action but at least 1 shared property: They work best when early detection of SMA enables affected patients to receive them sooner rather than later.

Prior to the approval of the first gene-modifying therapies for SMA—nusinersen (Spinraza; Biogen) in 2016, onasemnogene abeparvovec (Zolgensma; AveXis) in 2019, and risdiplam (Evrysdi; Genentech) most recently in August 2020, only supportive therapy was available and its timing did not alter the progressive loss of motor neurons in this autosomal recessive neurodegenerative disorder.

“Time is neurons,” commented Mary Schroth, MD, chief medical officer at Cure SMA, a national patient advocacy and education organization. “Both the treatments that are available are disease-modifying treatments. Neither of them are cures, but they are life-changing.”

Although SMA is the leading genetic cause of infant mortality, little progress had been made toward widespread newborn screening for early detection before the advent of gene therapies. The incorporation of SMA into newborn screening quickened with the evident success and FDA approval of nusinersen.

In response to encouraging data, the Maternal and Child Health Bureau of the Health Resources and Service Administration (HRSA) advised in 2018 that SMA be added to the Recommended Uniform Screening Panel (RUSP) in the United States.

“Based on what is known about screening and the risk of being born with SMA, experts think that screening all newborns in the United States for SMA would find about 36 babies with the disorder each year,” the HRSA report stated. “Each year, screening could prevent about 50 infants from needing a ventilator and about 30 deaths due to SMA Type 1.”

Inclusion in the RUSP does not mandate nationwide implementation, however, as implementation of the screen for newborns is determined by each state. According to tracking by Cure SMA, newborn screening for SMA has currently been adopted and implemented in 23 states, adopted but not yet implemented in 14 states, and undertaken as a pilot project in 3 states (FIGURE 1).

“Each state is independent in their identification of a specific SMA screening test, and the way that they go about launching it,” Schroth told NeurologyLive®. “In some states, it’s mandated by their state law that implementation occurs within a certain period of time after inclusion in RUSP.

“It is a state-by-state process,” she said, “which makes it challenging for patient advocacy organizations such as Cure SMA, and also for families because it may depend on which side of a state line you’re on as to whether the infant born today is screened or not for SMA.”

Initiatives from Cure SMA to promote newborn screening and early diagnosis include outreach to state legislators and public health laboratories, as well as maintaining an online newborn screening registry for data that could help support new therapy development and improve clinical care. One of its education programs, SMArt Moves, provides separate materials for families and for health care providers to increase knowledge about SMA and recognition of the disorder’s signs and symptoms.

With the increased emphasis on newborn screening for SMA that followed the advent of gene therapies, there has also been increased consideration of testing for carriers. Carrier testing for SMA had previously been recommended for all pregnant women by the American College of Medical Genetics and Genomics and the
In a recent article, bioethicists argued for increasing the availability of carrier screening to identify potential risk and inform family planning.\(^{10}\)

“The dual developments of increased treatment options for SMA, Zolgensma and Spinraza, and the increased sophistication of genetic screening technologies prompted us to look at this topic,” Christopher Gyngell, PhD, of the Department of Pediatrics at the University of Melbourne and the Murdoch Children’s Research Institute in Australia, told NeurologyLive\(^{®}\).

“These developments are leading to novel ethical challenges from both a clinical and policy standpoint,” Gyngell said.

In their analysis, Gyngell and colleagues argued that a moral imperative exists to pursue ex-ante interventions, such as carrier screening, in combination with prenatal testing and preimplantation genetic diagnosis or gene editing to reduce the incidence of SMA. They argue further that such ex-ante methods should be prioritized over ex-post methods for reasons related to autonomy, beneficence, and justice.

“One thing we touch on,” Gyngell commented, “is that carrier screening can lead to cost savings for health systems, which can be reinvested into other programs. Screening programs can therefore help build more sustainable health systems.”

**Treatment Recommendations Follow New Evidence**

The genetic screen for SMA is based on the determination that 95% of cases result from a homozygous deletion in the \(SMN1\) gene that encodes the survival motor neuron (SMN) protein. In the other 5% is a mutation rather than an \(SMN1\) deletion, which is not detected in screening.\(^{12}\)

The loss of SMN protein results in degeneration of anterior horn cells in the spinal cord, with resulting fatigue, paralysis, and atrophy of the proximal muscles.\(^{12}\) There is, however, an inherent mitigation, in that most individuals retain function of 1 or more copies of the paralogous \(SMN2\) gene.

\(SMN2\) also encodes the SMN protein, albeit in a lower amount.\(^{12}\) As the severity of the condition is related to the amount of available SMN, the severity is less in individuals with more copies of \(SMN2\) (Figure 2).\(^{12}\)

An SMA treatment algorithm based on early detection was developed through expert consensus by a working group convened in 2018 by Cure SMA.\(^{13}\) The group considered preclinical and clinical data (notably from presymptomatic infants in the ongoing NURTURE trial)\(^{14}\) to confirm that the best outcomes occur when disease-modifying therapy agents are given as early as possible.

They found strong evidence, however, that irreversible loss of motor neurons with SMA type 1 begins early in the perinatal period, “with severe denervation in the first 3 months and loss of more than 90% of motor units within 6 months of age.”\(^{13}\)

The working group recognized that the majority of infants with SMA who have 1 copy of \(SMN2\) would be symptomatic at birth, and they would be likely to have sustained loss that would not be remediated with disease-modifying therapy.

“In this case, the consensus is to defer to the attending physician to determine if the infant and family would benefit from treatment given his or her current disease state,” they indicated. “In the rare event that an infant with SMA with 1 copy of \(SMN2\) is truly presymptomatic, the strong consensus is that the infant should be treated immediately.”

The 2018 working group was unanimous in recommending that immediate, presymptomatic treatment should be provided for all infants with 2 or 3 copies of \(SMN2\). The group was split, however, on whether to extend that recommendation to infants with 4 or more copies.\(^{13}\)

They reached a consensus that infants with 4 or more copies of \(SMN2\) should be “screened carefully for the first presentation of symptoms” rather than receive gene-modifying therapy immediately after the condition is detected.

The working group was reconvened in 2019 to consider newly emerging data, including additional findings in the NURTURE trial that nusinersen treatment, when given to infants with 2 or 3 copies of \(SMN2\) who were aged under 6 weeks, was associated with significantly better outcomes than treatment given after the age of 6 weeks.\(^{15}\)

“Patients enrolled in this trial with 2 copies of \(SMN2\) have a
dramatically altered disease course with 100% alive, 100% sitting, 88% walking with assistance, 77% walking independently, and none needing the use of permanent ventilation assistance," the 2019 working group recounted.16

From these results, the group extrapolated that such outcomes were as likely to be attained in infants with 4 copies of SMN2 as in those with 3 copies. The working group now recommends that these infants also receive disease-modifying therapy while presymptomatic, immediately after detection in newborn screening.16

"With early treatment, disease should be mostly eradicated in presymptomatic patients with 4 copies of SMN2," they concluded.

Schroth emphasized that the rapid progress in treatment and notable clinical trial data that emerged after the first meeting had compelled the working group to reconvene.

“As a result of these therapies being available and clinical trials with additional treatments, clinicians have had more experience utilizing these treatments and understanding the risks and benefits,” she said. “There was a clear majority when they reconvened.”

Addressing, Averting a Devastating Course
SMA phenotypes have traditionally been categorized by the severity of symptoms and the age at onset, in the natural course without disease-modifying therapy, as well as by life expectancy and the motor function milestones that are attained.

In a 2020 journal article, Janbernd Kirschner, MD, of the Department of Neupediatric and Muscle Disorders at the Medical Center–University of Freiburg in Germany, and colleagues described the presentations associated with the traditional phenotypes, noting that the most severe, type 1, affects more than half of patients with SMA and manifests within the first 6 months of life.12

“A ‘floppy infant’ presentation, [with] reduced spontaneous movements, and a paradoxical breathing pattern are characteristic; these infants fail to achieve the free sitting milestone,” Kirschner and colleagues wrote. “SMA type 2 is characterized by a milder course,” they continued, “with onset of symptoms between the ages of 6 and 18 months. Per definition, these patients do manage free sitting, but not independent walking. The latter is achieved, at least temporarily in patients with SMA type 3, whose symptoms’ onset is during infancy or adolescence.

“In addition, some classifications define SMA type 0 and SMA type 4 with prenatal onset or a very mild phenotype entailing an adult onset of symptoms, respectively,” Kirschner and colleagues added.

They point out that disease-modifying drugs, age of onset, number of SMN2 copies, and the age at start of drug treatment will better define a clinical phenotype of SMA going forward than the traditional subtypes.

“These new disease trajectories also mean [that] we must modify and adapt the clinical approach taken,” they wrote.

This is especially relevant with the longer survival that is

**FIGURE 2. Classification of SMA Subtypes**

<table>
<thead>
<tr>
<th>SMN2 copy number(s)</th>
<th>SMA type #</th>
<th>Milestones achieved</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>no sitting</td>
<td>&quot;floppy infant&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulties in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>breathing and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>coughing, difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in swallowing, fasciculations</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>sitting, no walking</td>
<td>delay in motor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>development,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weakness, difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in coughing, joint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>contractures, scoliosis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>loss of abulation</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>independent walking</td>
<td>variable degree of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weakness, joint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>contractures, scoliosis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>loss of abulation</td>
</tr>
<tr>
<td>≥5</td>
<td>(IV)</td>
<td>independent walking</td>
<td>variable, but milder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weakness</td>
</tr>
</tbody>
</table>

SMA, spinal muscular atrophy; SMN2, survival motor neuron 2.

Figure reprinted with permission from Schorling et al (2020).12
achieved without ventilation support following initiation of drug treatment. This “needs to be considered when counseling the parents of patients with early-onset types of SMA,” they suggested.

Kirschner and colleagues also pointed out that, despite the improved survival and motor development of symptomatic patients with early-onset SMA, these children also exhibit a higher rate of scoliosis during the first years of life.

“Greater awareness of this risk, and close monitoring of spinal deformities, [appears] crucial to react early and enable the spine to be stabilized via medial orthosis,” they wrote.

Optimal long-term outcomes will require multidisciplinary care, according to Julie Parsons, MD, professor of clinical pediatrics and neurology and codirector of the Neuromuscular Clinic at the University of Colorado Anschutz Medical Campus/Children’s Hospital Colorado in Aurora.

“We are following them to see what that actually is going to mean and look like,” Parsons told NeurologyLive®. “So, it is important to have assessments by expert clinicians, in terms of looking at motor outcomes, pulmonary outcomes, growth and weight gain, bone health—we look at and monitor a number of different issues.

“We also have to remember the current population of patients—children and adults with SMA—and [they] can be extremely complex patients who may also benefit from some of the new therapies that are coming,” Parsons said, referring mainly to risdiplam, Roche/Genentech’s recently-approved therapy that has proved safe and effective in a wide range of patients with SMA, from infants to adults. The therapy, which was approved for use in adults and children with SMA types 1, 2, or 3 age 2 months and older,3 is an orally administered SMN2 splicing modifier associated with a range of benefits, including significant change in total Motor Function Measure 32 in younger patients and disease stabilization in older ones.17

In a recent review,18 Parsons and colleagues noted that updated standards of care19 offer 3 general phenotype categories that are determined by motor function class: nonsitters,itters, and ambulant. Each, they explained, has particular considerations and care needs.

“What I’m seeing is that these patients benefit from the new therapies. They continue to have enhanced motor skills,” Parsons said, “and, frankly, some of the children that we’ve followed have actually met normal motor milestones, the same as for a child who doesn’t have SMA.

“With early [disease-modifying] treatment, we don’t necessarily need to use nonoral therapy, such as feeding tubes, and the respiratory support may be less than what we would have needed in the previous standard of care,” Parsons said.

Schoth agreed that the treatment landscape has changed with the advent of new, effective therapies, and that this has posed both opportunities and challenges to professionals.

“There’s less confidence about what sort of intervention the baby will require,” she acknowledged. “And so now we’re in the stage of trying to better understand the impact of these treatments across the disease spectrum, and what things need to be carefully monitored and acted upon.”

REFERENCES


Selective Inverse Agonists of the Histamine 3 Receptor as Treatment for Narcolepsy

By Jennifer S. Sun, PhD

NARCOLEPSY IS A CHRONIC sleep disorder of autoimmune origin that affects roughly 1 in 2000 to 4000 individuals, occurring in men and women but with some variability in prevalence among racial and ethnic groups.1 It is characterized by excessive daytime sleepiness (EDS), sleep paralysis, hallucinations while falling asleep or waking, and, in some cases, sudden loss of muscle tone triggered by strong emotion (cataplexy), all symptoms that can seriously diminish quality of life.1 Comorbid neuropsychiatric manifestations in patients with narcolepsy (eg, eating disorders, depression, anxiety, and psychosis) often impair early diagnosis due to shared common features.2 To date, there are no treatments that hinder or slow disease development, but lifestyle changes and support groups have helped patients cope with narcolepsy. Medications that suppress sleepiness can also assist with managing symptoms, but careful selection and supervision are required due to the potent adverse effects (AEs) and addiction potential of most prescribed stimulants.1

Managing narcolepsy via behavioral strategies (eg, implementing good sleep hygiene and seeking counseling) to improve EDS may be challenging but has shown some added efficacy when combined with pharmacological treatment for EDS.1 Current treatments for narcolepsy symptoms include classic central nervous system (CNS) stimulants (eg, modafinil, amphetamines, sodium oxybate, and caffeine) to treat EDS and antidepressants (eg, fluoxetine, venlafaxine, or clomipramine) to treat cataplexy.1 These drug therapies may be costly and are sometimes associated with harmful AEs, including dependency; therefore, a need exists for narcolepsy treatments with improved safety and efficacy.

Narcolepsy is a chronic neurological condition affecting neurons in the hypothalamus that produce hypocretins 1 and 2 (also called orexins A and B, respectively),1 which can have severe consequences for the patient. Problems faced by patients with narcolepsy include social stigma associated with this disease, difficulties in obtaining an education and keeping a job, a reduced quality of life and socioeconomic consequences. Two subtypes of narcolepsy have been described (narcolepsy type 1 and narcolepsy type 2 Genetic analysis of individuals with narcolepsy has shown that lack of the peptide neurotransmitter hypocretin, a hallmark of this disease, is generally not caused by mutations in hypocretin-encoding genes. Instead, the approximately 70,000 hypothalamic neurons that produce hypocretin are lost in a process that is poorly understood but remarkably specific, sparing adjacent neurons that express melanin-concentrating hormone.3 This deficit in hypocretin neurons cannot be compensated for simply by administration of hypocretins because of their poor bioavailability. However, patients with narcolepsy have a documented 94% increase in the number of histaminergic neurons within the hypothalamic tuberomammillary nucleus; over time, this may compensate for the loss of hypocretin signaling.4 In fact, the brain histaminergic system controls several essential physiological functions, including arousal and maintenance of wakefulness.5 For these reasons, the histaminergic system has gained interest in narcolepsy research.


H3R, histamine H3 receptor.

Histamine, also known as the “waking amine,”7 mediates its effects through binding to 4 known G protein–coupled receptor subtypes, H1R to H4R. H1R, on the other hand, is predominantly expressed in the CNS, where it functions as a presynaptic autoreceptor to negatively regulate histamine synthesis and release,8,9 as well as a heteroreceptor to control the release of other neurotransmitters, such as acetylcholine, in various brain regions.10 Modulation of cortical activity and the sleep-wake cycle could therefore be achieved via H1R and its ligands.

Such histamine receptor ligands can be classified as agonists, neutral antagonists, or inverse agonists: agonists are ligands with a lower affinity for receptors in the uncoupled state, whereas the affinity of neutral antagonists is unaffected by the coupling state, and inverse agonists have a higher affinity for the uncoupled state of the receptor.11 Of significance to narcolepsy therapeutics and the treatment of brain disorders (eg, Alzheimer disease...
and schizophrenia) are inverse agonists of H₃R, it is especially important to suppress the relatively high constitutive activity of H₃R.¹¹ Inverse agonists of H₃R work by enhancing the release of histamine, which then competes with the ligand for occupancy of autoreceptors, thus inhibiting the constitutive activity of H₃R and stabilizing it in the inactive state (FIGURE).¹³

H₃R inverse agonists have had success in therapeutic management of behavioral deficiencies associated with schizophrenia in mouse models,⁹,¹¹ supporting the development of H₃R inverse agonists to treat EDS and cataplexy. Classic H₃R inverse agonists have been shown to increase wakefulness and to decrease sleep in rodent and feline models,¹⁴ although the effects are compound- and species-dependent.¹⁵ For example, the imidazole H₃R inverse agonists thiopera- mide and ciproxifan promote cortical activation and waking, whereas the H₃R agonists α-methylhistamine, imetit, and BP2-94 enhance cortical slow activity and increase slow-wave sleep.¹⁶ Based on these robust effects in animal sleep-wake control, H₃R ligands were investigate for treatment of human sleep-wake disorders, with the hope that these ligands would be H₃R specific, modulate only histamine neurotransmission, and promote effects on sleep-wake parameters that are comparable or even stronger than those of classic psychostimulants. Most chemical series currently under investigation are nonimidazole in nature, which provides advantages of being more selective for H₃R versus H₁R, H₂R, or H₄R, and increasing CNS penetration while minimizing drug-drug interactions.¹⁵

Pitolisant (Wakix; Harmony Biosciences) is a potent, orally available, once-daily, first-in-class, wake-promoting selective inverse agonist of H₃R with a good preclinical and clinical benefit to risk ratio for the treatment of narcolepsy.¹⁷ It was approved in the European Union in March 2016 for the treatment of narcolepsy with or without cataplexy in adults,¹⁸ and United States approval was granted in August 2019 for the treatment of EDS in adults with narcolepsy.¹⁹ Pitolisant functions by activating not only histaminergic and noradrenergic neurons but also the wake-promoting cholinergic and dopaminergic neurons.⁷ Results from pivotal, supportive phase 3 trials (HARMONY I, NCT01067222; HARMONY 1bis, NCT01638403) suggested that a dose of up to 40 mg per day for adults was significantly superior to placebo for enhancing wakefulness and decreasing cataplexy rate, although pitolisant was comparable to modafinil in management of EDS.²⁰

Pitolisant was demonstrated to have minimal risk of abuse in preclinical and clinical studies, and it remains the only antinarcoleptic drug not scheduled as a controlled substance in the United States.²⁰ In the HARMONY CTP (NCT01800045) and HARMONY I (NCT01067222) trials, no patients on pitolisant experienced amphetamine-like withdrawal syndrome during the withdrawal phase, whereas this AE occurred in several patients treated with modafinil.²¹,²² Patients taking pitolisant also did not experience hypersomnia or fatigue upon treatment interruption, and Beck Depression Inventory scores improved significantly from baseline compared with placebo (P = .02).²³ Blood chemistry and hematological and cardiovascular parameters were consistent with those of controls.²¹ Overall, pitolisant was well tolerated in clinical trials, with participants typically experiencing few AEs, primarily headache, insomnia, nausea, and anxiety, which are consistent with its mechanism of action.²⁰,²³ Long-term safety data for pitolisant in individuals with narcolepsy are currently limited to the HARMONY III trial in adults (NCT01399606),²⁴ with a complementary prolonged open-label study ongoing in pediatric patients (NCT02611687).

Other H₃R inverse agonists have been evaluated in clinical trials for treatment of narcolepsy. The efficacy of GSK189254 was similar to that of modafinil in terms of increased wakefulness, reduced slow-wave sleep, and decreased paradoxical sleep in mice,²⁵ although a phase 2 clinical trial (NCT00366080) was terminated based on the interim results of a futility test.²⁶ A phase 2 study (NCT00424931) of a new formulation of modafinil, JNJ-17216498, was conducted based on promising preclinical data for a related compound, JNJ-5207852, which demonstrated increased wakefulness and a favorable pharmacokinetic profile in mice.²⁷ Although the clinical trial was completed in 2007, no additional information has been released since 2014. Preclinical data for SUVN-G3031 showed increased wakefulness in a rat model of narcolepsy.²⁸ In 2 phase 1 clinical studies (NCT02342041 and NCT02881294), single doses up to 20 mg and multiple doses up to 6 mg once daily were found to be safe and well tolerated in healthy human subjects, with no effects of age, sex, or fasting status on the agent’s pharmacokinetics and safety profile.²⁹ An ongoing phase 2 study evaluating SUVN-G3031 safety and efficacy in patients with narcolepsy began in September 2019 (NCT04072380).

In conclusion, narcolepsy is a condition of sleepiness for which lifelong treatment is likely to be required. Promising advances involve using novel agents to treat targeted symptoms such as EDS, with the potential to treat more than 1 symptom of narcolepsy. However, cost, convenience, and AEs remain challenges. Furthermore, although the beneficial effects of pitolisant in EDS and cataplexy treatment are well substantiated, the use of H₃R inverse agonists in cognitive disorders is promising but requires further testing.
Approaching Multiple Sclerosis With a Global Perspective

A group of international experts in the treatment of multiple sclerosis offer their varying viewpoints on the history, identification, and management of the disease.

By Matt Hoffman

AVOIDING SILOED THINKING ALSO applies to medical decisions. Much of the information in treatment guidelines and medical textbooks is based on varied experiences and reports, brought together to help form a collective opinion. Knowledge to be gained from the experience of others is especially meaningful in a disease where treatment optimization is a work in progress. Although many treatments exist for multiple sclerosis (MS), the decision to pursue one treatment over another can often be enhanced based on the experiences of our peers and their patients.

Differences in treatment, from drug availability to strategy, are especially apparent across international borders, where usage and clinical guidelines may vary. In MS, there are clear departures in diagnostic and treatment guidelines between those set forth by various clinical governing bodies; these are exacerbated by differences in drug approval patterns by the US FDA and the European Medicines Agency (EMA), as well.

In an effort to capture these differences and learn from them in a leveled environment, NeurologyLive® recently brought together a panel of international MS experts for a Peer Exchange titled “Global Approaches to the Management of Relapsing Multiple Sclerosis.” Led by Fred Lublin, MD, the Saunders Family Professor of Neurology and director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai Medical Center in New York, the panelists discussed their experiences managing MS across the spectrum, beginning in a logical place: differentiation.

Clinically Isolated Syndrome Versus Multiple Sclerosis

In 2017, the latest update to the McDonald diagnostic criteria made for more clear and concise decision-making, especially between patients who should be treated with disease-modifying therapies (DMTs) and those who should not—particularly in the instance of patients with clinically isolated syndrome (CIS) compared with those with a confirmed MS diagnosis.

“In Germany, we had an ongoing discussion when we still worked with the concept of CIS and early relapsing-remitting MS, and since we have the new criteria, my idea is that the group of patients with CIS is now much smaller,” Sven Meuth, MD, PhD, of the University of Münster in Germany, said. “This is also why we don’t have to discuss any more that some of the platform therapies are only approved for relapsing-remitting MS, but not for CIS.”

Meuth explained that when the updated criteria were published and adopted, ongoing discussion surrounding CIS and early stage MS was halted because of the criteria’s allowance for a better opportunity to diagnosis these patients with relapsing-remitting MS earlier, and thus begin treatment earlier in instances where previously they may have hesitated. Wallace Brownlee, MBChB, PhD, of the National Hospital
for Neurology and Neurosurgery in London, United Kingdom, echoed Meuth's sentiments about the update to the McDonald criteria as helpful for earlier diagnosis, which he said “open up new therapeutic opportunities for patients with relapsing MS.”

This has not necessarily been the case across the globe. Patricia K. Coyle, MD, of Stony Brook Neurosciences Institute in Stony Brook, New York, noted that in the United States there is an important distinction that had allowed for high-risk CIS patients to be treated.

“Granted, greater than 50% of first-attack patients will meet the 2017 criteria,” Coyle noted. “But if you have a first attack and you fit for high risk for MS, and you’ve ruled out other things, you basically have relapsing MS. That’s your first attack, whether you met the criteria or not. We can treat those patients in the United States.”

Lublin concurred that in his experience, CIS has been treated without difficulty in the US even prior to the official recognition of CIS as a condition. Aside from those with particularly aggressive cases, these patients are often given the CIS label. Lublin noted that physicians often do not distinguish a difference between the first and subsequent attacks, but with regulatory agencies and authorities, that was not always the case.

Following an earlier update to the criteria in 2010, a rather large change to how physicians viewed dissemination in time was made, thereby allowing a single MRI to identify the dissemination. This, Lublin said, dropped the prevalence of CIS by about 50% because patients were now meeting criteria for MS and could be treated as such. Whether a similar difference was brought on by this latest update or not, remains to be seen.

“Some very early data that have come out of the Netherlands have shown that perhaps up to 70% of patients can now be diagnosed confidently with MS at the time of the first clinical attack that is highly suggestive of relapsing MS, like optic neuritis or partial myelitis,” Brownlee said.

The First-, Second-, Third-Line Concept

Once a patient has been properly identified and diagnosed with MS, the process is not clear-cut and simple. With a large armamentarium of DMTs to choose from, deciding which therapy is best for an individual patient can be a daunting task. As such, the community built out a designation system for a number of agents, denoting them as first-line, second-line, and third-line agents.

This system was developed to help physicians pick the best treatment for their patients as more are diagnosed earlier in the disease process. However, the concept has its flaws. “I don’t like the concept of first line, second line, third line. We should be able to use any agent that we feel is the best choice in our patient initially,” Coyle said.

First-line treatments often consist of injectable agents—varieties of glatiramer acetate and interferon-beta—and Coyle noted that she considers a number of oral agents to be first line, save for cladribine (Mavenclad; EMD Serono), a recently approved immune reconstitution therapy that is not recommended for patients’ first attack on its FDA label.

“I think it could be, but that’s bending the curve a little,” Coyle noted. “Then, when we go to the infusible agents—the monoclonal antibodies—I think they’re all first line with the exception of mitoxantrone, which we basically never use in the United States, and alemtuzumab, which has been recommended on the US label as a third-line agent. I feel very comfortable using the orals, using several of the monoclonals and infusibles, and certainly the injectables as first-line agents.”

Meuth agreed with Coyle, adding that physicians need freedom to decide which agent is best for a given patient. He noted that at his institution, the University of Münster, the MS center does have the freedom to operate outside of the first-, second-, and third-line concept. But it is complicated because of several factors outside the physician’s control.

“When it comes to reimbursement, the office-based neurologists are not allowed to go on these treatments, and this is why we are a little bit limited, based on this reimbursement situation,” Meuth said. “From the pathophysiology behind it, I cannot agree more. If we have a given patient with a highly active disease, we should not play around with something like platform therapies, but we should be able to start with a monoclonal, for instance.”

Meuth explained that community clinicians in these instances are allowed to start with a high-efficacy agent only when the patient is highly active themselves. They are required to have 9 or more T2 lesions on magnetic resonance imaging (MRI) and more than 2 relapses coinciding with progression on the Expanded Disability Status Scale (EDSS).

“I think you will agree that this is far too late to quantify these patients as highly active,” he posed to the group.

Additionally, the designation of a therapy as a first-, second-, or third-line agent can differ globally. Meuth mentioned fingolimod (Gilenya; Novartis), which in the United State is considered a first-line agent, but in Europe has been approved for use only in those highly active patients. “This is a difference, and this brings me to the approval of new sphingosine 1-phosphate (SIP) modulators. But in the majority of patients, we have to start with platform therapy or first-line therapy, and then we can have this escalation concept, and this is, in my opinion, not the way to go,” he said.

In the United Kingdom, Brownlee added, neurologists are increasingly initiating intensive therapies early on in those with newly diagnosed relapsing MS. He explained that alemtuzumab (Lemtrada; Sanofi) was used extensively as a first-line agent prior to the recent suspension and investigation from the EMA. Now, it is mainly used as a later therapy in those who have continued to experience relapses and/or MRI activity on a first-line treatment.

Those first-line treatments include the oral agents dimethyl fumarate (Tecfidera; Biogen) and teriflunomide (Aubagio; Sanofi), and increasingly ocrelizumab (Ocrevus; Genentech) or cladribine—though not fingolimod.

“Fingolimod, like in Germany, is reserved for patients who are second line or very highly active, and that’s really on the basis of concerns around the time it was licensed over cardiac safety,”
Brownlee said. “I must say with long-term clinical experience with this drug, that has become less of an issue, and it’s become clear that really that is a problem only with the first dose.”

Some very early data that have come out of the Netherlands have shown that perhaps up to 70% of patients can now be diagnosed confidently with MS at the time of the first clinical attack that is highly suggestive of relapsing MS, like optic neuritis or partial myelitis.

— WALLACE BROWNLEE, MBCHB, PHD

Global Use of Interferon in MS
Historically, interferon-beta has played a pivotal role in the treatment of MS. Now considered a first-line therapy, it was among the first agents approved to treat the disease in the US and throughout the world.

Meuth explained that 2 decades ago when it first entered the market, it was the go-to therapy in Germany. Now, its use has become generally limited to those who have remained stable on an interferon over the years. “Never change a winning team,” he said. But for those who are newly diagnosed, interferon has lost its go-to status as a first-line agent.

“Since the approval of the oral agents, electromagnetic fields, and teriflunomide, we don't find too many patients starting with interferons anymore,” he said. “There’s a significant decrease in the usage of interferons. For newly diagnosed patients, they are looking, at least in our country, more for the oral agents, so there is a development in this injectable market, I have to say.”

Lublin asked about the role mechanism of action has played in that shift at his institution, and Meuth noted that it has to some extent, and that he and his colleagues seek to keep things simple for patients. With interferons, that includes talking about a shift from type 1 helper T-cell responses toward type 2 helper T-cell responses, but he acknowledged that the effects contributing to the mechanism of action of interferons are various.

“If we have the pathophysiology of MS in mind, we can nearly say that each and every step in this whole cascade is somehow impacted by interferon. It alters the cellular recognition by a modulation of major histocompatibility complex class 2 and the T-cell receptor,” Meuth said. “It reduces, thereby, lymphocyte activation and proliferation, but it has also an impact on the transmigration over the blood-brain barrier from the periphery to the central nervous system.”

Some data suggest that in the central nervous system, this process leads to a downregulation of pro-inflammatory cytokines, and it shifts—though not in a fashion entirely understood—the differentiation toward the type 2 helper T cells, giving it a “very broad mechanism of action,” Meuth said.

Brownlee explained that, similar to other countries, the use of interferon as a first-line DMT in the United Kingdom is on the downward slope. In recent years, the regulatory agency has taken action on updating the label for interferon with regard to pregnancy in Europe, which has allowed the therapy to find its place in the landscape.

Now, physicians in Europe have the option to treating women who are planning to become pregnant, or are pregnant and breastfeeding, on the basis of observational studies suggesting the safety of those approaches. Additionally, interferons and the other injectable therapies also have a role to play for those with certain comorbidities that complicate treatment with other DMTs.

“I recently saw a patient who'd had a renal transplant, so they were immunosuppressed on 2 immunosuppressive medications and low dose steroids, and they developed relapsing-remitting MS on top of that,” Brownlee said. “One of the injectable agents, the patient in this case went for interferon, is a good option because you don't need to worry about drug interactions or immunosuppressive effects.”

The case has been similar in the US, with the usage of interferons being much lower than when they entered the market. Coyle explained that in her experience, their use has been comparable to that of Germany—those who are on it and doing well remain unless a significant adverse event (AE) arises.

“I haven't started many patients with interferon, but I have individuals who I’ve been treating since November 1993 when we first got interferon beta-1b, and they've done spectacularly well. As we know with all of these agents, there are some people who have responded to all of them, and I think 'don't change a winning team’ was pretty much the logic,” Lublin said.

To watch this entire Peer Exchange series, go to neurologylive.com/link/195.
Indication
Nurtec ODT is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use
Nurtec ODT is not indicated for the preventive treatment of migraine.

Select Important Safety Information
Contraindications: Hypersensitivity to Nurtec ODT or any of its components.

Please see additional Important Safety Information and the accompanying Brief Summary of Full Prescribing Information on the following pages.
IMPORTANT SAFETY INFORMATION

Contraindications: Hypersensitivity to Nurtec ODT or any of its components.

Warnings and Precautions: If a serious hypersensitivity reaction occurs, discontinue Nurtec ODT and initiate appropriate therapy. Serious hypersensitivity reactions have included dyspnea and rash, and can occur days after administration.

Adverse Reactions: The most common adverse reaction was nausea (2% in patients who received Nurtec ODT compared to 0.4% in patients who received placebo). Hypersensitivity, including dyspnea and rash, occurred in less than 1% of patients treated with Nurtec ODT.

Drug Interactions: Avoid concomitant administration of Nurtec ODT with strong inhibitors of CYP3A4, strong or moderate inducers of CYP3A or inhibitors of P-gp or BCRP. Avoid another dose of Nurtec ODT within 48 hours when it is administered with moderate inhibitors of CYP3A4.

Use in Specific Populations: Pregnant/breast feeding: It is not known if Nurtec ODT can harm an unborn baby or if it passes into breast milk. Hepatic impairment: Avoid use of Nurtec ODT in persons with severe hepatic impairment. Renal impairment: Avoid use in patients with end-stage renal disease.

Please see Brief Summary of Full Prescribing Information on the following page.

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**
(For complete product information, see Full Prescribing Information.)

**NURTEC™ ODT (rimegepant) orally disintegrating tablets 75 mg, for sublingual or oral use**

1 INDICATIONS AND USAGE

NURTEC ODT is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use:

NURTEC ODT is not indicated for the preventive treatment of migraine.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of NURTEC ODT is 75 mg taken orally. The maximum dose in a 24-hour period is 75 mg. The safety of treating more than 15 migraines in a 30-day period has not been established.

4 CONTRAINDICATIONS

NURTEC ODT is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or any of its components. Delayed hypersensitivity has occurred (see Warnings and Precautions (5.1)).

5 WARNING AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including dyspnea and rash, have occurred with NURTEC ODT in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. If a hypersensitivity reaction occurs, discontinue NURTEC ODT and initiate appropriate therapy (see Contraindications (4)).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

• Hypersensitivity Reactions (see Warnings and Precautions (5.1))

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of NURTEC ODT has been evaluated in a randomized, double-blind, placebo-controlled trial (Study 1) in 682 patients with migraine who received one 75 mg dose of NURTEC ODT. Approximately 85% were female, 74% were White, 21% were Black, and 17% were Hispanic or Latino. The mean age at study entry was 40 years of age (range 18-75 years of age).

Long-term safety was assessed in an open-label extension study using a different oral dosage form of rimegepant. That study evaluated 1,798 patients, dosing intermittently for up to 1-year, including 1,428 patients who were exposed to rimegepant 75 mg for at least 6 months, and 863 who were exposed for at least one year, all of whom treated an average of at least two migraine attacks per month.

The most common adverse reaction in Study 1 was nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo).

Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT (see Contraindications (4) and Warnings and Precautions (5.1)).

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure. Avoid concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4.

Concomitant administration of NURTEC ODT with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4.

7.2 CYP3A4 Inducers

Concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A4 can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy of NURTEC ODT. Avoid concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A4.

7.3 Transporters

Rimegepant is a substrate of P-gp and BCRP efflux transporters. Concomitant administration of NURTEC ODT with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant exposure. Avoid NURTEC ODT with inhibitors of P-gp or BCRP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary:

There are no adequate data on the developmental risk associated with the use of NURTEC ODT in pregnant women. In animal studies, oral administration of rimegepant during organogenesis resulted in adverse effects on development in rats (decreased fetal body weight and increased incidence of fetal variations) at exposures greater than those used clinically and which were associated with maternal toxicity. The evaluation of developmental effects following oral administration of rimegepant throughout pregnancy and lactation was inadequate (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated rate of major birth defects (2.2 to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations:

Disease-AssOCIated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

8.2 Lactation

There are no data on the presence of rimegepant or its metabolites in human milk, the effects of rimegepant on the breastfed infant, or the effects of rimegepant on milk production. There are no animal data on the excretion of rimegepant in milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NURTEC ODT and any potential adverse effects on the breastfed infant from NURTEC ODT or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects. Clinical studies of NURTEC ODT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dosage adjustment of NURTEC ODT is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Plasma concentrations of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment. Avoid use of NURTEC ODT in patients with severe hepatic impairment.

8.7 Renal Impairment

No dosage adjustment of NURTEC ODT is required in patients with mild, moderate, or severe renal impairment. NURTEC ODT has not been studied in patients with end-stage renal disease and in patients on dialysis. Avoid use of NURTEC ODT in patients with end-stage renal disease (ClCr < 15 mL/min).

10 OVERDOSAGE

There is limited clinical experience with NURTEC ODT overdosage. Treatment of an overdose of NURTEC ODT should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. No specific antidote for the treatment of rimegepant overdose is available. Rimegepant is unlikely to be significantly removed by dialysis because of high serum protein binding.

Manufactured for:

Biohaven Pharmaceuticals, Inc.

New Haven, CT 06510 USA

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Telemedicine, Technology, and the Future of Alzheimer and Dementia Care

By Matt Hoffman

ALTHOUGH 2020 HAS PRESENTED the medical community with many unique challenges and required adjustments to care, clinicians have sought to focus on the silver linings, instead.

The rapid transition to a telemedicine-based model of care now provides many elderly patients and their caretakers with an easier way to connect with their physicians and health care team. From the provider perspective, this window into a patient’s home life also has its advantages, as it allows for additional observations and guidance for improved care and well-being.

In an interview with NeurologyLive®, Howard Fillit, MD, founding executive director and chief science officer of the Alzheimer’s Drug Discovery Foundation, and clinical professor of geriatric medicine and palliative care, medicine, and neuroscience at Mount Sinai School of Medicine, discussed the impact that the coronavirus disease 2019 pandemic has had on dementia care and the long-coming updates to the care model that it has actually helped to ignite.

Q: What advantages does telemedicine offer to the Alzheimer disease community?

Telehealth has been percolating along for decades now, but this has really just accelerated the adoption of it in medical practice, and I think in a really good way. It’s going to change the future of how we practice medicine, and I think it’s a good thing for geriatric patients in general. I’m a geriatrician. These patients are often frail, they have multiple comorbidities, many of them are in living in poverty, and even just to get to the doctor is tough. Especially for someone with Alzheimer disease and their loved ones, their caregivers.

Getting dressed, getting in the taxi in confusing environments, getting to the waiting room, sitting in the waiting room—all that stuff is hard for a lot of patients with Alzheimer disease. Same with getting in the car if you’re in suburbia or outside the cities, so I think that telehealth is a big advantage for patients with Alzheimer disease. I hope that, going forward, especially with new payment models for telemedicine, that this will be encouraged.

The kind of questions that patients often ask of doctors in the care of patients with Alzheimer disease are often about care and management. We do have medications that are modestly effective, but certainly most of the questions that I get are about care and management of patients and advice to caregivers. It can be very effectively delivered on a telemedicine platform—and when I say telemedicine, I include the old-time technology that we call the phone. We don’t have to have video conferencing to give advice. I have gotten phone calls from stressed out caregivers asking “What should I do? What should I do about this?” and in the extreme, sometimes, it requires medication, for agitation for example, but I definitely think that Alzheimer disease can be effectively managed with the advice of physicians through technology platforms.

Q: Have you encountered any challenges with applying telemedicine?

The main challenge, which I don’t see as a big challenge, is incorporating telemedicine and especially video conferencing. We all do phone calls. Doctors often say, “OK, I’ll take your phone calls from 8 AM to 9 AM, and then I have to see patients,” but with video conferencing, you really have to sit there and [go] face-to-face [with patients]. It’s managing and figuring out how to incorporate telemedicine into the workflow of the day. That’s the biggest challenge, setting aside time for video conferencing with patients and doing scheduling.

The other thing is that patients with Alzheimer disease can often be confused, and I think actually seeing the patient through a video...
Telehealth has been percolating along for decades now, but this has really just accelerated the adoption of it in medical practice, and I think in a really good way. It's going to change the future of how we practice medicine, and I think it's a good thing for geriatric patients in general.

— Howard Fillit, MD

At the Alzheimer's Drug Discovery Foundation, through our work with the Diagnostics Accelerator and Bill Gates and his organization, we're looking at incorporating all kinds of other technologies besides video conferencing in order to better evaluate a patient with Alzheimer disease. Things like evaluating speech and language, motion detectors and looking at how people move around, and all kinds of other symptoms that we can detect with new technology. The video conferencing and the telemedicine—it's just 1 aspect of how technology will be used in the future care of patients with Alzheimer. There will be many other platforms, including computerized cognitive testing. Testing that you can do on your phone to see how a patient's doing and these other aspects of behavior that will help us with early diagnosis, to ramp up and improve the rigor and efficiency and cost of clinical trials, and bring new drugs to market for Alzheimer disease.

Q: What do you foresee as the future impact of teledmedicine care?

To me, it's amazing. Honestly, I remember when we got our first TV in 1953. That's where I'm coming from. I was only 5 years old then, but it's just amazing. To apply that to health care now, I really do think it's going to change things. It'll make health care more efficient, more effective, and it's also from your point of view of peer to peer. In geriatric medicine, we often have family conferences, and often, families these days are all over the country—all over the world. I've had family conferences already to discuss a particular issue regarding a patient with Alzheimer disease with a video conference that included someone from California, Florida, New York, and Paris all in 1 place. That wouldn't have happened if we had to do it physically. It could have been done on telephone, but I don't think it has the same impact. There's no turning back at this point. Telemedicine is going to be a vital part of geriatric care and of health care in general.
In June, Amylyx announced that it had completed enrollment and dosing in 96 of the previously planned 100 participants in the phase 2 PEGASUS trial (NCT03533257), which will assess the safety, tolerability, drug target engagement, and neurobiological effects of treatment with AMX0035 in patients with early dementia due to Alzheimer disease (AD) or late mild cognitive impairment (MCI).1

AMX0035 is a first-in-class investigational therapy designed to reduce neuronal death and dysfunction. It targets mitochondrial and endoplasmic reticulum-dependent neuronal degeneration pathways through a combination of sodium phenylbutyrate and tauroursodeoxycholic acid—a treatment developed using the rationale of successful tandem therapies in HIV, cancer, and heart disease.

“In sporadic Alzheimer disease, for example, dysfunction in these pathways can be both a cause and consequence of amyloid-beta and tau pathologies, driven by a host of other cellular, genetic and environmental factors,” Steven E. Arnold, MD, PEGASUS principal investigator and translational neurology head of the Interdisciplinary Brain Center at Massachusetts General Hospital and Harvard Medical School, told NeurologyLive®.

The eligibility criteria for the 24-week, randomized, double-blind, placebo-controlled study is purposefully broad, which will allow the study to “assess the biological effects of AMX0035 across the disease spectrum,” Arnold said. “Further appreciating the heterogeneity of Alzheimer disease, we allow a diverse set of supporting biomarkers to determine Alzheimer’ disease diagnostic eligibility. Our hope was that this would open our study up to patients often ineligible for other trials while providing deep phenotypic insight into patients with a combination of neuroimaging, plasma, and spinal fluid biomarkers and multisequence MR imaging.”

Those eligible for inclusion in the study are between age 55 and 89, with Montreal Cognitive Assessment (MoCA) scores between 8 and 26 and a Geriatric Depression Scale score of less than 7. Patients with any central nervous system (CNS) disease other than Alzheimer disease or mild cognitive impairment are excluded from the trial (FIGURE).

In addition to safety and tolerability, the study will focus on several disease-relevant brain biomarkers that be will be evaluated on both a composite and individual level. “These include cognition with established neuropsychological assessment and interview measures, hippocampal structure and function with MR neuroimaging, and cerebrospinal fluid and plasma amyloid, tau, and neurodegeneration biomarkers,” Arnold said, adding that the research teams will also examine more exploratory markers of inflammation and metabolism, as well. “Understanding how the drug may be working, and if a particular subset of patients is especially responsive in the phase 2 study, will allow us to tailor the design of a phase 3 study.”

The 2-drug combination approach makes AMX0035 1 of the more distinguished drugs making its way through the Alzheimer disease pipeline. Arnold relayed that sodium phenylbutyrate is used in urea cycle abnormalities but also crosses the blood-brain barrier and is a histone deacylase inhibitor. One of its main functions is to suppress the unfolded protein response which is overactive in AD. Tauroursodeoxycholic acid stabilizes mitochondrial membranes, thus improving the bioenergetics of cells. It can reduce or make cells more resistant to oxidative stress, while also working as a neuroprotectant by preventing apoptosis, he said.

“We recognize that there are a lot of mechanisms that are driving neurodegeneration in Alzheimer [disease], and if you just hit 1 thing and others are left unaddressed, you may have some very modest benefit, but you may have no benefit because everything else is working against the cell,” Arnold told NeurologyLive®. “By combining drugs to ameliorate the damaging effects of these different mechanisms that are active, overactive, or abnormally active in Alzheimer disease, we have a better chance of rescuing sick and dying cells.”

Confidence in the combination drug has only been bolstered by results from Amylyx’s CENTAUR trial (NCT03127514), where treatment with AMX0035 has been shown to be associated with a statistically significant (P < .05) slowing of amyotrophic lateral sclerosis disease progression based on change from baseline on the ALS Functional Rating Scale-Revised.2

Results from the PEGASUS trial are expected to be released in the first quarter of 2021. “We will work to accelerate patient access to AMX0035 according to any requirements issued by the FDA,” Arnold said.
Unraveling Autoimmune Epilepsy

Could expanding insights into the pathophysiology of autoimmune epilepsy offer seizure-free hope for patients?

By Nicola Davies, PhD

ALTHOUGH THERE HAVE BEEN relatively effective treatments for seizures since 1912, beginning with phenobarbital, the focus on the symptoms of epilepsy rather than the cause means that many patients with difficult to treat epilepsy still long for effective therapies. This is especially the case for autoimmune epilepsy, an under-recognized condition that is often unmanageable with conventional antiseizure medications. As a result, a truly “seizure-free” life has remained out of reach for many. This may be set to change as researchers continue to uncover the causes of different types of epilepsy and the mechanisms of action of different treatment modalities.

“Autoimmune epilepsy is essentially a seizure disorder where a neural-specific antibody is present, may be pathogenic, and may cause seizures,” said Lindsay Higdon, MD, a neurologist and epilepsy specialist at Jefferson University Hospital in Philadelphia, Pennsylvania. In one study, experts found that approximately 20% of unexplained epilepsy cases had evidence of circulating neural antibodies, suggesting an autoimmune cause. These antibodies can target antigens present on neural surfaces or within the neural cell.

Over the past decade, several neural surface antigens and intracellular antigens have been found and documented in patients presenting with epilepsy, and in 2017, autoimmune epilepsy was officially recognized as a distinct entity by the International League Against Epilepsy.

When to Suspect Autoimmune Epilepsy

“There are several clues,” Sarosh Irani, BMBCh MA (Oxon), DPhil, head of the Oxford Autoimmune Neurology Group and associate professor at Oxford University in the United Kingdom, told NeurologyLive®. “These patients often present with an explosive onset, and a higher frequency of seizures than normal.” Most of these patients also present with other features of autoimmune encephalitis, such as memory disturbances, mood changes, and changes in personality. Some patients experience faciobrachial dystonic seizures, which are essentially diagnostic of an underlying antibody.

Patients with autoimmune epilepsy can also show characteristic MRI findings that are consistent with limbic encephalitis. A retrospective cohort study found that such patients usually demonstrated parenchymal atrophy that was disproportionate to age, or T2 hyperintensities in cortical or subcortical regions.

To help clinicians make an early and accurate clinical diagnosis, Divyanshu Dubey, MBBS, and a team of investigators at...
Mayo Clinic have developed and validated a predictive tool.1,4 The APE (Antibody Prevalence in Epilepsy of unknown etiology) score takes into consideration the onset and progression of the seizure disorder, clinical signs, and MRI and cerebrospinal fluid (CSF) findings. If the APE score is greater than 4, there is a high chance that the epilepsy is of autoimmune origin.

One of the main hallmarks of autoimmune epilepsy is that it is generally resistant to antiepileptic drugs. In a systematic review of 6 studies that included 169 patients with autoimmune epilepsy, antiepileptic drugs were effective in only 10.7% of cases.5 “Antiepileptic drugs may still be effective in a few cases, but they treat the symptom of the autoimmune condition, and not the cause,” Higdon said.

Getting to the Root of the Problem
Once the cause is known, it makes sense to treat autoimmune epilepsy just like other autoimmune diseases—by modulating the immune system. “Along with antiepileptic drugs, we use either steroids, intravenous immunoglobulin (IVIG), or plasma exchange,” Higdon said. “All 3 treatments decrease immune-mediated inflammation in the central nervous system by suppressing or changing the immune system or removing antibodies.” Indeed, one study showed that immunomodulatory therapy led to a 19-fold increase in odds of a better seizure outcome, with plasmapheresis (odds ratio [OR], 32.5) proving to be more effective than intravenous steroids (OR, 8.25).1 In another study, about 75% of patients became seizure-free in the 2 months after starting immunotherapies.6

Many researchers are exploring IVIG—a concentrate of human antibodies obtained from healthy donors—as an alternative to steroids and plasmapheresis. Its administration is a simpler procedure compared with plasmapheresis and can help avoid the adverse effects of steroid therapy.

This form of treatment—flooding the body with more antibodies—may seem counterintuitive. However, IVIG is believed to stabilize and strengthen the immune system. How does this happen? “Currently, no one can answer that accurately, but there are a few hypotheses,” said Irani. “The IVIG possibly saturates the immune system, preventing key causative antibodies like leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 immunoglobulin G (CASPR-2) from functioning. IVIG antibodies could also directly interfere with these antibodies, or with their targets.”

A recent randomized controlled trial conducted at Mayo Clinic provided further evidence that IVIG was effective in reducing seizures in a cohort who met criteria for autoimmune epilepsy.7 Patients who tested positive for LGI1 antibodies and CASPR-2 were enrolled in the study. Of 8 patients enrolled in the IVIG arm, 6 showed more than 50% improvement in seizure frequency compared with none in the placebo group. After 5 weeks, 6 patients in the placebo arm of the trial who had persistent seizures were switched to IVIG; 4 of these then reported more than 50% improvement in seizure frequency. IVIG is still a relatively new treatment strategy and needs more research before it is adopted as the main modality of treatment. “We don’t know how it accesses the central nervous system, and how it affects B cells that produce target antibodies,” Irani said. “Assessing these factors could help identify groups of patients who would respond better to treatment.” Indeed, not all studies have shown favorable results with IVIG. For instance, one study showed a poor response rate in patients who tested positive for antiglutamic acid decarboxylase 65 antibodies (GAD-65); only about 32% of these patients responded to treatment with IVIG.8

Higdon clarified that the kind of antibody present could influence response to immunotherapy. “While antibodies to neural surface antigens (such as LGI1 and CASPR2) may respond well to immunotherapy, antibodies to intracellular antigens (like GAD-65) are less responsive,” she said. “This is because these antibodies may not be the cause of seizures, but more an epiphenomenon—a secondary symptom that occurs simultaneously with a condition but is not directly related to it.”

In a retrospective study of 50 patients, researchers showed that those who had antibodies to a neural surface antigen, the voltage gated potassium channel complex antigen, were more likely to become seizure-free compared with patients who had GAD-65 antibodies (FIGURE).9 Notably, those with antibodies to intracellular antigens may benefit from the addition of cytotoxic chemotherapy.

To predict which patients are more likely to respond to immunotherapy, Dubey and his team have also introduced and validated the RITE (Response to Immunotherapy in Epilepsy) score.4 This takes into account all the factors of the APE score, whether immunotherapy was started within 6 months of seizure onset, and, in addition, whether or not a neural antibody has been detected in

**FIGURE. Response to Therapy by Antibody Status**

Ab negative, negative to antibody testing; AED, antiepileptic drug; GAD65, glutamic acid decarboxylase 65; VGKC-complex, voltage-gated potassium channel-complex.
plasma or CSF. Patients with a RITE score greater than 7 are more likely to respond to immunotherapy.

While IVIG may potentially be more convenient and safer compared with steroids and plasmapheresis, well-designed comparative studies are currently lacking. “Based on my current clinical experience, it is likely that steroids and plasma exchange will prove to be more effective,” Irani said. This opinion is partially shared by Higdon. Often, she said, “the response is transient and there needs to be repeated infusions or more aggressive immunotherapy with cyclophosphamide or rituximab.”

Antiepileptic drugs may still be effective in a few cases, but they treat the symptom of the autoimmune condition, and not the cause.”

— LINDSAY HIGDON, MD

Applying a Robust Management Algorithm

Many patients with autoimmune epilepsy can be successfully managed if a proper algorithm is followed, such as the one suggested by Higdon. 10 “The first step, when you deal with a patient who has epilepsy of unknown origin, is to apply the APE score. If it is greater than 4, neural antibody testing should be carried out,” Higdon said. “Immunotherapy should ideally be initiated even before the antibody test results are received, either with steroids or IVIG.” She suggested that plasmapheresis be reserved for patients who fail to respond to previous treatments, or who have severe symptoms. If the antibody tests reveal the presence of an intracellular antigen, tumor screening must additionally be considered.

Of course, this fundamental algorithm does not cover all bases. “The ideal protocol for the duration of treatment and evaluation of response still needs to be developed,” Higdon said. It is also unclear if antiepileptic drugs can be tried again, if immunotherapy fails. In a retrospective study, a small proportion of patients did respond to antiepileptic drugs after immunotherapy had failed. 8

The researchers stated that certain antiepileptics, like carbamazepine, also had immunomodulatory properties, and this dual effect could have been responsible for a seizure-free response in a small subset of patients.

Most experts feel that a better understanding of the pathophysiology of autoimmune epilepsy is the way forward. “We are currently focusing on how the B cells produce antibodies, and how these antibodies interfere with target antigens,” said Irani, whose most recent research has focused on exploring the characteristics and pathogenic potential of the LGI1 antibody. Understanding these key mechanisms could pave the way to establishing innovative methods of blocking the antibody effects.

REFERENCES

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

Victories are personal for the 10,000+ who have been treated with SPINRAZA worldwide.1*

- FOR US PATIENTS TAKING SPINRAZA -

>40% of patients taking SPINRAZA are adults†

>90% of patients who started SPINRAZA remain on treatment1†

3-80 Days

Has treated SMA in patients 3 days† to 80 years old1,2,†§

INDICATION
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

*Based on commercial patients, early access patients, and clinical trial participants through December 2019.
†Based on commercial patients in the US (including Puerto Rico) through December 2019.
‡Includes clinical trial patients.
§Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.
Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

Learn more at SPINRAZA-hcp.com

IMPORTANT SAFETY INFORMATION (continued)
Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

Please see full Prescribing Information at SPINRAZA-hcp.com.

As a courtesy, our full Prescribing Information is also available en Español. For prescribing decisions, please refer to official approved labeling.

References: 1. Biogen Data on File [as of 12/19]; 2. SPINRAZA [prescribing information].

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225 Binney Street, Cambridge, MA 02142
1 INDICATIONS AND USAGE
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION
2.1 Dosing Information
SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage
The recommended dosage is 12 mg (5 mL) per administration.

Initiate SPINRAZA treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose
If a loading dose is delayed or missed, administer SPINRAZA as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

2.2 Important Preparation and Administration Instructions
SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation
• Store SPINRAZA in the carton in a refrigerator until time of use.
• Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use external heat sources.
• Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored. The use of external filters is not required.
• Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
• Administer SPINRAZA within 4 hours of removal from vial.

Administration
• Consider sedation as indicated by the clinical condition of the patient.
• Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
• Prior to administration, remove 5 mL of cerebrospinal fluid.
• Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation [see Adverse Reactions (6.3)].

2.3 Laboratory Testing and Monitoring to Assess Safety
Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:
• Platelet count
• Prothrombin time; activated partial thromboplastin time
• Quantitative spot urine protein testing

3 DOSAGE FORMS AND STRENGTHS
Injection: 12mg/5mL (2.4mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia and Coagulation Abnormalities
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.
5.2 Renal Toxicity
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of SPINRAZA-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS
The following serious adverse reactions are described in detail in other sections of the labeling:
- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of SPINRAZA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to SPINRAZA in 260 patients (48% male, 80% Caucasian), including 227 exposed for at least 6 months and 181 exposed for at least 1 year. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 to 16 years of age at first dose) with symptomatic SMA; in a sham-controlled trial in infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=84 for SPINRAZA, n=42 for control); in open-label studies in presymptomatic and symptomatic infants (n=40); and in open-label studies in later-onset patients (n=56). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)
In Study 1, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in Study 1 were infants, adverse reactions that are verbally reported could not be assessed in this study.

Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Infantile-Onset SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg(^1) N=80 %</th>
<th>Sham-Procedure Control N=41 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory infection(^2)</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\) Loading doses followed by 12 mg (5 mL) once every 4 months

\(^2\) Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenzal, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis
In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

**Clinical Trial in Later-Onset SMA (Study 2)**

In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain.

**Table 2. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Later-Onset SMA (Study 2)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg¹</th>
<th>Sham-Procedure Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=84 %</td>
<td>N=42 %</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

### 6.2 Immunogenicity

As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to nusinersen in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenic response to nusinersen was determined in 249 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Sixteen patients (6%) developed treatment-emergent ADAs, of which 3 were transient, 13 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, “persistent” is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.

8.2 Lactation
Risk Summary
There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established (see Clinical Studies (14.1)).

Juvenile Animal Toxicity Data
In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use
Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs (see Warnings and Precautions (5.1)).

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity (see Warnings and Precautions (5.2)).

Manufactured for:
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Cambridge, MA 02142
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Addressing the Invisible Symptoms of Parkinson Disease

Although motor signs are the major focus of clinical treatment, symptoms affecting behavior are often ranked by patients as the most disruptive aspects of their disease.

By Linda Peckel

ALTHOUGH PARKINSON DISEASE (PD) could be characterized as a very visible neurologic disorder, with tremors, gait issues, and other physical complications recognizable to the untrained eye, many, including affected patients, are unaware of some of the more invisible symptoms driven by underlying changes to the central nervous system.

These nonmotor symptoms can include “mood disorders, rapid eye movement behavioral sleep disorder, depression and anxiety, cognitive impairment, hallucinations, and psychosis,” according to Jill Giordano Farmer, DO, MPH, assistant professor of neurology at Drexel College of Medicine in Philadelphia, Pennsylvania, and director of the Parkinson’s Disease & Movement Disorder Program at the Global Neurosciences Institute in New Jersey. “But when you’re specifically talking about disruptive behavioral issues in Parkinson disease, the focus becomes agitation, psychosis, and issues with hallucinations or delusions.”

The rates of behavioral symptoms in PD have not been fully profiled but represent a significant burden both earlier and later in the course of the disease.1 Farmer observed that the patterns vary substantially among patients. “There’s definitely that idea that, ‘If you’ve seen one PD patient, you’ve seen one PD patient,’” she said. “They present similarly, but each with a nuanced set of symptoms that are most problematic for them.”

About 45% of patients with PD who reside in nursing homes were shown to have symptoms of depression, which is the most commonly reported neuropsychiatric symptom, followed by irritability and apathy.2 Dementia in PD is estimated to occur in up to 30% of patients, with symptoms that can include apathy, hallucinations, and delusions,3 but as a single symptom, psychosis with or without dementia are experienced at some point by up to 50% of patients with PD, Farmer said.

Hallucinations

By far the most problematic hallucinations are visual, Farmer said. “They’re usually formed visions of people, children or animals, but they don’t engage with the individual.” The frequency varies from every once in a while to several times a day. “When it happens suddenly or out of the blue, you want to make sure you’re not dealing with an underlying infection,” she noted. “Urinary tract infections are notorious for exacerbating or uncovering hallucinations in Parkinson patients, but that’s not disease progression.”
Farmer observed that true PD-related hallucinations usually occur slowly and insidiously, “patients may describe a presence or seeing something out of the corner of their eye, something they’re not sure they saw, but when they looked away and then looked back the vision was gone.” She pointed out that early on, they don’t persist. “Usually the time from the first mention to persistent hallucinations is on the order of years not months. Once the doctor is made aware, it becomes a symptom that is monitored since it will impact decision-making for how Parkinson symptoms will be managed going forward,” she said.

Although hallucinations are an adverse effect to many medications used to treat PD, they tend to appear more frequently in advanced disease even without medications, according to Michelle Lavallee Dagostine, MD, a movement disorder specialist at Hartford Healthcare Chase Family Movement Disorders Center in Connecticut. “It is possible to have hallucinations when you are not taking any medications at all, but the medications have the potential to make it worse,” Dagostine told NeurologyLive®. “This is why it is so important to have open conversations with the entire treatment team so that we are aware of all symptoms and can manage them accordingly.” Physicians should be cognizant of PD medications that can exacerbate hallucinations and be diligent about reviewing other medications prescribed by the patient’s care team for other conditions in order to avoid or modify drug regimens that can predispose patients to hallucinations (TABLE).

The suspect nature of hallucinations means they often go unreported. This can be because patients are afraid of changes to their medication regimens that are otherwise working for them, but more often they are afraid of the stigma such a symptom may bring. “The way that we manage that is that we ask every time, ‘What kinds of things are you seeing that are not really there?’” she explained. “We normalize it to take away any embarrassment and then we treat it when present.”

To address these concerns, the conversation often centers around a multipronged approach with both behavioral strategies and pharmacologic ones. “Up until a few years ago, we had to borrow from psychiatry to treat psychosis in PD and patients had good reason to be concerned with taking these medications because they block dopamine which is obviously the last thing you want to do with a Parkinson patient because it can worsen their motor symptoms,” Farmer said. “So often we would reduce Parkinson disease medications that were keeping their motor symptoms in check,” she added. “We have a new drug available to us that is specific for Parkinson delusions and psychosis with Nuplazid (pimavanserin; Acadia). This medication is unique because it does not work on dopamine, but serotonin, which has been shown to play a significant role in PD psychosis. Since it only works on serotonin and not dopamine, it does not impact motor symptoms.”

Apathy

Patients frequently develop apathy as part of the natural course of the disease.4 “It comes on so slowly that it’s really unrecognizable.

Table. Parkinson Disease Medications Associated With Hallucinations

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Drug class</th>
<th>Dopamine precursors</th>
<th>Dopamine agonists</th>
<th>Anticholinergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbidopa-levodopa (Rytary; Duopa)</td>
<td>Dopamine precursors</td>
<td>amphetamine hydrochloride (Apokyn)</td>
<td>trihexyphenidyl (Artane)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rotigotine transdermal system (Neupro)</td>
<td>benztrpine (Cogentin)</td>
<td></td>
</tr>
<tr>
<td>pramipexole dihydrochloride (Mirapex; Mirapex ER)</td>
<td>Dopamine agonists</td>
<td>amantadine (Osmolex; Gocovri)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ropinirole extended-release tablets (Requip XL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>apomorphine hydrochloride (Kynmobi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amantadine (Osmolex ER; Gocovri)</td>
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</tr>
</tbody>
</table>

You have people who are typically very high functioning and who were quite motivated before the onset of their disease, who lose their drive,” said Dagostine. “That motivational component has been disrupted, and they do not have the initiative to start an activity or seek out opportunities that may be beneficial. Dopamine plays a role in the motivation pathway so that when you lose the normal levels of the chemical, you may also lose motivation as well.”

With a mean reported prevalence of 35% in PD,4 apathy represents one of the greatest challenges to clinicians, according to Dagostine. “When people with Parkinson start losing that motivation, they stop doing things that are in their best interest in general, but also for their disease.” They may not be as proactive with things like exercise, or setting their alarms to take their medications. They may frustrate their care partners by not taking advantage of opportunities to learn about their disease through classes and lectures and support groups,” she noted. “It’s challenging from a patient’s perspective, but also for the family.”

Mood Disturbances

Over the long course of PD, patients often develop some form of depression or anxiety, and it will look different for each patient. “It can be waves of feeling overwhelmed, darkness or sadness, or mood may change when medications wear off,” Dagostine said, noting that “PD is a disorder not only of dopamine levels, but also of serotonin and norepinephrine. I tell my patients that it’s unlikely that they will be able to avoid having some level of depression or anxiety during their lifetime. That would be like jumping in a pool and not getting wet. You simply don’t have the neurotransmitters you need to feel like your normal self.”

Treatments for Behavioral Symptoms

Limited pharmacologic therapies are available for behavioral symptoms of PD, and many other interventions are often added to reduce those symptoms’ impact on the patient and family.

“Treatment of Parkinson disease can be complex in that it may involve addressing the behavioral changes in addition to the movement disorder that may be associated with neurochemical changes.”

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happening in the brain on an organic level,” Victoria Pena-Cardinali, LCSW, a psychotherapist and clinical coordinator at Capital Health Behavioral Health Specialists in New Jersey, told NeurologyLive®. “A comprehensive approach is needed for an accurate assessment and effective formulation of a treatment plan.” Part of Pena-Cardinali’s assessment includes patient safety and access to resources. She also works to reduce social isolation and encourage participation in normal life activities. “This is crucial for the psychological health of the person with Parkinson disease,” she added.

Dagostine reported that treatment of behavioral nonmotor symptoms is handled at her institution by a multidisciplinary team, involving a doctor of naturopathic medicine, a nutritionist, and the use of nonpharmacologic therapies including reiki, massage, acupuncture, and guided meditation. “We offer these along with a variety of group classes and opportunities for exercise. Movement in general can be extremely helpful and can be done in a variety of ways to meet people’s needs and abilities,” she said. “Treatment does not have to entail medications, although in many cases they are useful. We also have a psychiatrist on staff who helps patients navigate this option if and when appropriate.”

“I also think we need to consider changes in functional ability related to cognitive decline that require adjusting to new ways of interacting with the world,” Pena-Cardinali said. “These adjustment difficulties may have a negative impact on the patient’s mood and their relationships, and they can contribute to further disability.”

Ultimately, it’s important that each patient is addressed as an individual with unique attention given to their most immediate needs. This starts by building rapport and focusing on more concrete goals for daily coping, and then moves on to more advanced goals about values, relationships, and communication. “Patients develop an increased level of awareness about the relationship between their changing emotional needs and their movement disorder that helps ease the distress and reduces catastrophic thinking about their disease,” Pena-Cardinali said.

A major benefit to comprehensive therapy is that it helps the patient gain an empowering new sense of control in their lives that instills hope. After treatment, patients are more skillful in the management of their depression and/or anxiety symptoms and have increased distress tolerance and coping capacity.

“One of the biggest problems with Parkinson disease is that it steals from you so slowly that most times, people are unaware of the changes,” said Dagostine. “At some point, your brain really is disconnected from your body, not only on a motor level, but also on an emotional level. It’s our job to seek out these symptoms so that we can treat them and improve people’s quality of life.”

REFERENCES
Closing the Treatment Gap in Progressive MS

New biomarkers of disease activity may help better vet investigational therapies aimed at slowing the insidious neurodegeneration seen in primary progressive multiple sclerosis.

Tori Rodriguez, MA

IN RECENT DECADES, the development of therapies for patients with relapsing-remitting multiple sclerosis (RRMS) has significantly progressed, with FDA approval of numerous anti-inflammatory disease-modifying therapies (DMTs). However, advances in drug development for progressive forms of MS—affecting an estimated 10% to 15% of patients with MS—have lagged considerably in comparison.1

“Disease modification for progressive MS continues to be challenging,” said Kathleen Costello, MS, a board-certified adult nurse practitioner and MS nurse specialist as well as the National Multiple Sclerosis Society’s associate vice president of healthcare access. “Most current therapies that are FDA approved for relapsing forms of MS include ‘active secondary progressive MS’ in the approval, but that implies that there is ongoing inflammation as seen on MRI or presenting as a relapse,” she told NeurologyLive®, whereas primary-progressive MS (PPMS) is characterized by steadily worsening neurologic function with no relapses.

This treatment gap is largely attributed to the continued lack of clarity regarding the mechanisms that drive disease activity in PPMS and secondary-progressive MS. Disease progression has been cited as the main contributing factor in MS-related disability accumulation, further underscoring the need for effective treatment strategies for the disease’s progressive forms.2

“I think the biggest challenge in treating progressive MS is understanding its pathophysiology,” said Robert J. Fox, MD, staff neurologist at the Mellen Center for Multiple Sclerosis and vice-chair for research at the Neurological Institute of Cleveland Clinic in Ohio. “What is truly driving the insidious decline? Is it compartmentalized inflammation? A metabolic derangement? A mitochondrial dysfunction? At this point, we really don’t know.”

While it is understood that relapses in RRMS are driven by inflammation due to infiltration of peripheral leukocytes across the blood-brain barrier into the central nervous system (CNS), the relationship between inflammation and the blood-brain barrier in progressive MS is less clear.3 Historically, MS research has focused predominantly on the relapsing phase of MS, in which relapses and inflammation can be assessed on MRI.4 In progressive MS, the lack of specific biomarkers and outcomes measures have presented barriers to the development of new therapies.2

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Compartmentalized Inflammation

The available evidence suggests that "progressive MS is characterized by ongoing inflammation that occurs within the CNS, with an intact blood-brain barrier," according to Costello. "There appear to be more activated microglia as well as involvement of T and B lymphocytes in progressive MS, and there is evidence of mitochondrial and axonal damage from reactive oxygen species and nitrogen species, which can lead to neurodegeneration."

The compartmentalized inflammation associated with progressive MS may limit or preclude the effectiveness of anti-inflammatory DMTs that have shown promise in RRMS.4

"Currently, where there is ongoing inflammation, we know that stopping the infiltrating inflammation with anti-inflammatory therapies can be helpful—at least, modestly helpful," Fox told NeurologyLive®. Aside from this benefit, the effects of such therapies on progressive MS pathologies remain unclear. "If there is no active infiltrative inflammation, the potential benefits of anti-inflammatory therapies are modest, with risks often outweighing them."

In research described in 2019 in the European Journal of Neurology, investigators from the MSBase cohort study conducted an analyses of pooled data (n = 1284) to examine the effects of anti-inflammatory DMTs approved for RRMS and used off-label to treat progressive MS.5 The MSBase team found that these agents had no substantial effect on the short- to medium-term disability outcomes of progressive MS patients, as indicated by a lack of significant difference between treated and untreated patients in the hazard ratios of 3-month confirmed Expanded Disability Status Scale (EDSS) progression events (HR, 1.0; 95% CI, 0.6–1.7; P = .87), confirmed EDSS improvement (HR, 1.0; 95% CI, 0.6–1.6; P = .91), or reaching a confirmed EDSS step ≥7 (HR, 1.1; 95% CI, 0.7–1.6; P = .69).

Ocrelizumab, currently the only FDA-approved agent to treat PPMS, is the only therapy thus far that has demonstrated efficacy in reducing the accumulation of disability in this patient population. In the results of the phase 3 ORATORIO trial of 732 patients with PPMS, published in 2017 in the New England Journal of Medicine, the primary end point of confirmed disability progression at 12 weeks was observed in 32.9% of patients taking ocrelizumab compared with 39.3% of those in the placebo arm (HR, 0.76; 95% CI, 0.59–0.98; P = .03).5

In terms of secondary end points, confirmed disability progression at 24 weeks was noted in 29.6% of those taking ocrelizumab versus 35.7% with placebo (HR, 0.75; 95% CI, 0.58–0.98; P = .04); also, performance on the timed 25-foot walk declined by 38.9% with ocrelizumab versus by 55.1% with placebo (P = .04). In addition, there was a 3.4% reduction in the total volume of brain hyperintense T2 lesions on MRI with ocrelizumab compared with a 7.4% increase with placebo (P <.001), and brain volume decreased by 0.90% with ocrelizumab versus 1.09% with placebo (P = .02).

Patients taking ocrelizumab experienced more frequent infusion-related reactions, upper respiratory tract infections, oral herpes infections, and neoplasms, compared with placebo. Rates of serious adverse events and serious infections did not differ significantly between groups.

"While these results are modest, they do indicate a place for ocrelizumab in the treatment of some individuals with PPMS," Costello said.

Future Directions

Many researchers are trying "to better understand the true driving pathophysiology of progressive MS," said Fox. "Once that is better understood, it should be easier to develop therapies for it."

To effectively guide the development of new treatment strategies, Costello said that the immunopathological mechanisms involved in progressive MS, as well as mechanisms that inhibit remyelination, would certainly change the treatment paradigm in progressive MS" and improve disease stability, she said, allowing patients to participate in desired activities.

Potential therapies under investigation include agents to inhibit microglial activation and reduce oxidative stress. Additionally, researchers are currently aiming to identify the most appropriate biomarkers to use in screening progressive MS therapies. In this area, a wide range of potential measures may indicate disease progression, including plasma neurofilament light chain levels, unique volatile organic compounds in the breath, and other MRI, blood, and cerebrospinal fluid biomarkers.

"At this point, imaging biomarkers appear to hold the most promise in progressive MS," said Fox. "Cortical atrophy and magnetization transfer ratio (MTR) imaging appear to have good reproducibility and dynamic change over time. The phase 2 SPRINT-MS trial found both of these to be particularly powerful in measuring the effect of ibudilast in progressive MS."7

The estimated rate of annual change in MTR over the 96-week study period was −0.0282 with placebo and −0.0051 with ibudilast (difference, 0.0231; 95% CI, 0.0003–0.0458). For cortical thickness, the estimated rate of annual change was −0.0105 with placebo and −0.0019 with ibudilast (difference, 0.0086; 95% CI, 0.0028–0.0144). "These markers may allow for smaller, shorter, and more efficient phase 2 trials in the future," Fox said.

"Progressive forms of MS present increased challenges due to the accumulation of disability, which may include difficulties with mobility, cognition, balance, or other symptoms, leading to greater challenges with maintaining employment and other role responsibilities," Costello explained. "These complex issues require a coordinated and comprehensive approach that may include rehabilitation, mental health, neuropsychology, vocational rehabilitation, and others to optimize function and ability to participate."

Costello noted that not all practices have access to the resources listed above. To help, the National Multiple Sclerosis Society has a staff of highly trained MS Navigators available to partner with health care providers and patients to provide support, identify resources, and assist with job challenges and disability affecting individuals with progressive MS. ■

For a full list of references, see the article on NeurologyLive.com
AT THE HELM

Mitchell S.V. Elkind, MD, MS, Is Named AHA President

The American Heart Association (AHA) has named neurologist Mitchell S.V. Elkind, MD, MS, the president of the organization for its 2020-2021 fiscal year, which began July 1. Elkind recently chaired the AHA Advisory Committee while also serving as president-elect from July 2019-June 2020. He is a professor of neurology and epidemiology at Columbia University in New York, New York, and is the second neurologist to serve as AHA president in the organization’s 95-year history. With Elkind’s rise, the organization said they hope to expand their focus on stroke and brain health in addition to its previous dedication to cardiovascular diseases. The Harvard Medical School graduate, who also trained in internal medicine at Brigham and Women’s Hospital and in neurology at Massachusetts General Hospital in Boston, Massachusetts said in a statement that he hopes to bring “more neuroscientists, both basic and clinical, into the American Heart Association family.”

RESEARCH REWARDS

American Headache Society Names Annual Award Winners

Richard B. Lipton, MD, FAHS, the Edwin S. Lowe chair in neurology and vice chair of the Saul R. Korey Department of Neurology at Albert Einstein College of Medicine, and director of the Montefiore Headache Center, both in New York, New York, was recently presented with the American Headache Society’s (AHS) Lifetime Achievement Award, typically given to a member who has sustained prolonged service to the AHS over their lifetime and is considered the society’s highest honor. Among the many other distinguished AHS award winners are Dawn C. Buse, PhD, FAHS, clinical professor of neurology at Albert Einstein College of Medicine; and Stewart J. Tepper, MD, FAHS, professor of neurology at Geisel School of Medicine at Dartmouth College, both of whom received the Above & Beyond Award, which is given to AHS members who have provided significant service during the past 1 to 2 years.

NIH Awards Grant to Develop Personalized MCI Treatment

The National Institutes of Health have awarded Ying-hui Chou, ScD, an investigator in the Department of Psychology at the University of Arizona in Tucson, with a $3.4 million grant to learn more about how to prevent memory loss and enhance brain function in patients experiencing mild cognitive impairment (MCI). Chou, director of the Brain Imaging and Transcranial Magnetic Stimulation Laboratory and assistant professor of cognition and neural systems, will aim to combine transcranial magnetic stimulation (TMS) with brain imaging techniques to develop a personalized, noninvasive treatment for people with MCI. The therapy will target the hippocampus in hopes of improving symptoms of cognitive decline in patients with amnestic MCI. TMS therapy is FDA approved for certain conditions including obsessive-compulsive disorder, depression, and migraine.

Stanford’s Alzheimer’s Disease Research Center Is Awarded $15M

The National Institute on Aging has awarded Stanford Alzheimer’s Disease Research Center $15 million to continue their translational research on improving the diagnosis, treatment, and prevention of Alzheimer disease and similar cognitive disorders. The award is a 5-year renewal of a $7.3 million grant the center received in 2015. Victor W. Henderson, MD, MS, director of the center and professor of neurology and neurological sciences, and associate director Katrin Andreasson, MD, professor of neurology and neurological sciences, have led a staff of more than 50 members to conduct research on Alzheimer disease, Parkinson disease, and related disorders. A recent research project funded in part by the grant helped Tony Wyss-Coray, PhD, the D.H Chen Professor in neurology and neurological sciences, and his colleagues to identify immune cells in the blood and cerebrospinal fluid specifically associated with Alzheimer disease.

Helena M. Blumen, PhD, Receives $3.5M to Study Brain Changes in Aging

Cognitive neuroscientist Helena M. Blumen, PhD, of Albert Einstein College of Medicine, has received a 5-year, $3.5 million grant from the National Institutes of Health to study how changes in the brains of older adults affect gait, cognition, and the development of dementia. The study will feature 200 older adults and will use brain MRI to measure structural and functional changes in regions that control gait, sensory perception, and executive functions. Assessments such as timed walking tests will measure changes in gait while other established measures will evaluate memory, processing speed, executive function, and other cognitive abilities. Blumen’s new pursuit hopes to further explore the link between declining gait speed, cognitive decline, and dementia. Notably, the 200 participants in Blumen’s new study have already been enrolled in the LonGeneity study, which has focused on genetic and biochemical markers associated with exceptional longevity.

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