Optimizing the Migraine Consultation

BY MARSHALL C. FREEMAN, MD, FAHS, FAAN, FAANEM

Accessible Stroke Care for Diverse Populations: The Montefiore Approach
BY LAUREN CHAMBERLAIN, DO; AND ANDREW SPECTOR, MD

Patient Evaluation for Excessive Daytime Sleepiness
BY LAUREN CHAMBERLAIN, DO; AND ANDREW SPECTOR, MD

A New Approach to Protein Misfolding in Parkinson Disease
BY MANOLO BELLOTTO, PHD

S1P Receptor Modulation in Multiple Sclerosis
BY JENNIFER S. SUN, PHD

CLINICAL VIEWPOINT
Improving Stroke Systems of Care: A Tandem Role for Neurology and Primary Care Physicians
WITH MITCHELL S.V. ELKIND, MD, MS, MPHIL
The first and only short-course oral RMS treatment with demonstrated efficacy over 96 weeks with a maximum of 20 days of treatment, MAVENCLAD offers:\(^1,^2\):

- A well-characterized safety and tolerability profile\(^2\)
- Proven efficacy at 96 weeks\(^1,^2\)
- Lymphocyte depletion followed by repopulation, without continuous immunosuppression\(^1,^3,^4\)

**INDICATION**

MAVENCLAD\(^5\) (cladribine) tablets is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

**IMPORTANT SAFETY INFORMATION**

**WARNING: MALIGNANCIES and RISK OF TERATOGENICITY**

- Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant.

**CONTRAINDICATIONS**

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

**RMS:** relapsing multiple sclerosis.

*Screening and monitoring should be performed before, during, and after treatment. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is administered in 2 treatment courses approximately 1 year apart.\(^1\)
MAVENCLAD ® (cladribine) tablets is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

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The first and only short-course oral RMS treatment with demonstrated efficacy over 96 weeks with a maximum of 20 days of treatment, MAVENCLAD offers 1,2:

A well-characterized safety and tolerability profile

Proven efficacy at 96 weeks 1,2

Lymphocyte depletion followed by repopulation, without continuous immunosuppression 1,3,4

* Screening and monitoring should be performed before, during, and after treatment. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is administered in 2 treatment courses approximately 1 year apart. 1

MOVE FORWARD WITH CONFIDENCE

MAVENCLAD demonstrated efficacy across endpoints

ARR (primary endpoint) 1,2

RELATIVE REDUCTION IN ARR AT 96 WEEKS

58% vs placebo (P=0.001)

0.14 MAVENCLAD (n=433) vs 0.33 placebo (n=437)

EDSS progression 1,2

REDUCTION IN RISK OF 3-MONTH CONFIRMED EDSS PROGRESSION

33% vs placebo

13% MAVENCLAD (n=433) vs 19% placebo (n=437); HR 0.67*

T1-Gd+ lesions 1,2

REDUCTION IN MEDIAN NUMBER OF T1-Gd+ LESIONS

0 MAVENCLAD (n=433) vs 0.33 placebo (n=437); (P<0.001)

REDUCTION IN MEAN NUMBER OF T1-Gd+ LESIONS

86% RELATIVE REDUCTION (P<0.001)

REDUCTION IN MEDIAN NUMBER OF ACTIVE T2 LESIONS

0 MAVENCLAD (n=433) vs 0.67 placebo (n=437); (P=0.001)

REDUCTION IN MEAN NUMBER OF ACTIVE T2 LESIONS

73% RELATIVE REDUCTION (P<0.001)

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; HR: hazard ratio; T1-Gd+: T1 gadolinium-enhanced.

*Includes data from studies of oral and parenteral forms of MAVENCLAD.

Learn more about MAVENCLAD, prescribed to 33,000+ patients globally in real-world settings, at MAVENCLAD.com/hcp

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.
WARNINGS AND PRECAUTIONS

• Malignancies: Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

• Risk of Teratogenicity: MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD closing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.

• Lymphopenia: MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.

• Infections: MAVENCLAD can reduce the body’s immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncological indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.

• Hematologic Toxicity: In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.

• Risk of Graft-versus-Host Disease With Blood Transfusions: Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.

• Liver Injury: In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.

• Hypersensitivity: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

• Cardiac Failure: In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Adverse Reactions: The most common adverse reactions with an incidence of >2.0% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Acute short-term therapy with corticosteroids can be administered.

Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.

Screening and monitoring should be performed before, during, and after treatment.

MAVENCLAD and the MAVENCLAD logo are trademarks of Merck KGaA, Darmstadt, Germany, or its affiliates.

MAVENCLAD® (cladribine) tablets, for oral use
Read the Full Prescribing Information before use.

WARNING: MALIGNANCIES AND RISK OF TERATOGENICITY

Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with an increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD (see Contraindications (4) and Warnings and Precautions (5.1)).

Risk of Teratogenicity

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for feto
data. Malformations and embryopathy occurred in animals. Exclude pregnancy before the first start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant (see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)).

4 CONTRAINDICATIONS

MAVENCLAD is contraindicated:

• in patients with current malignancy (see Warnings and Precautions (5.1)),
• in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. May cause fetal harm (see Warnings and Precautions (5.1)).
• to patients with a history of hypersensitivity to cladribine (see Warnings and Precautions (5.8)).

5 WARNINGS AND PRECAUTIONS

5.1 Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients (10 events in 3,754 patient-years [0.27 events per 100 patient-years], compared to placebo patients [3 events in 2,217 patient-years [0.13 events per 100 patient-years]). Malignancy cases in MAVENCLAD patients included metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer, compared to malignancy cases in placebo patients, all of which were curable by surgical resection (basal cell carcinoma, cervical carcinoma in situ [2 cases]). The incidence of malignancies in United States MAVENCLAD clinical study patients was higher than the rest of the world (6 events in 1,936 patient-years [2.21 events per 100 patient-years] compared to 0 events in United States placebo patients; however, the United States results were based on a limited amount of patient data. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years (see Dosage and Administration [2.2]). In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy (7 events in 790 patient-years [0.91 events per 100 patient-years]) calculated from the start of cladribine treatment (see Table 4). The risk of malignancy with reinstituting MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with an increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD. (see Contraindications (4) and Warnings and Precautions (5.1)).

5.2 Risk of Teratogenicity

MAVENCLAD may cause fetal harm when administered to pregnant women. Malformations and embryopathy occurred in animals (see Use in Specific Populations (8.1)). Advise women of the potential risk to a fetus during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment (see Use in Specific Populations (8.1, 8.3)). MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception.

5.3 Lymphopenia

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. In patients treated with a cumulative dose of MAVENCLAD 3.5 mg/kg over 2 courses as monotherapy, 26% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter; median time to recovery to at least 800 cells per microliter was approximately 28 weeks. Additive hematologic adverse reactions may be expected if MAVENCLAD is administered prior to or concomitantly with other drugs that affect the hematologic profile (see Drug Interactions (7.3)). The incidence of lymphopenia less than 500 cells per microliter was higher in patients who had used drugs to treat relapsing forms of MS prior to study entry (32.1%), compared to those with no prior use of these drugs (23.8%).

Obtain complete blood count (CBC) with differential including lymphocyte count prior to, during, and after treatment with MAVENCLAD. (see Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.4) for timing of CBC measurements and additional instructions based on patients’ lymphocyte counts and clinical status (e.g., infections)).

5.4 Infections

MAVENCLAD can reduce the body’s immune defense and may increase the likelihood of infections. Infections occurred in 48% of MAVENCLAD-treated patients compared to 44% of placebo patients in clinical studies. The most frequent serious infections in MAVENCLAD-treated patients included herpes zoster and pyelonephritis (see Herpes Virus Infections). Fungal infections were observed, including cases of coccidiomycosis. HIV infection, active tuberculosis, and active hepatitis must be excluded prior to initiation of each treatment course of MAVENCLAD (see Contraindications (4)).

Consider a delay in initiation of MAVENCLAD in patients with an acute infection until the infection is fully controlled. Initiation of MAVENCLAD in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended (see Drug Interactions (7.1)). Concomitant use of MAVENCLAD with these therapies could increase the risk of immunosuppression.

5.5 Hepatic Tuberculosis

Three of 179 (1.7%) cladribine-treated patients in the clinical program developed tuberculosis. All 3 cases occurred in regions where tuberculosis is endemic. One case of tuberculosis was fatal, and 2 cases resolved with treatment. Perform tuberculosis screening prior to initiation of the first and each subsequent treatment course of MAVENCLAD. Latent tuberculosis infections may be activated with use of MAVENCLAD. In patients with tuberculosis screening of MAVENCLAD until the infection has been adequately treated.

Hepatitis

A clinical study patient died from fulminant hepatitis B infection. Perform screening for hepatitis B and C prior to initiation of the first and second treatment course of MAVENCLAD. Latent hepatitis infections may be activated with use of MAVENCLAD. Patients who are carriers of hepatitis B or C virus may be at risk of irreversible liver damage and failure by hepatitis reactivation. In patients with hepatitis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Herpes Virus Infections

In controlled clinical studies, 8% of MAVENCLAD-treated patients developed a herpes viral infection compared to 2% of placebo patients. The most frequent types of herpes viral infections were herpes zoster infections (3.0% vs. 0.2%) and oral herpes (2.6% vs. 1.2%). Serious herpes zoster infections occurred in 0.2% of MAVENCLAD-treated patients. Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.

The incidence of herpes zoster was higher during the period of absolute lymphocyte count less than 500 cells per microliter, compared to the time when the patients were not experiencing this degree of lymphopenia. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Patients with lymphocyte counts below 500 cells per microliter should be monitored for signs and symptoms suggestive of infections, including herpes infections. If such signs and symptoms occur, initiate treatment with acyclovir as indicated. Consider interruption or delay of MAVENCLAD until resolution of the infection.

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 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.

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with parenteral cladribine for oncologic indications, cases of PML have been reported in the postmarketing setting.

Obtain a baseline (within 3 months) magnetic resonance imaging (MRI) before initiating the first treatment course of MAVENCLAD. At the first sign or symptom suggestive of PML, withhold MAVENCLAD and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

Vaccinations

Administer all vaccinations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD, because of a risk of active vaccine infection (see Herpes Virus Infections). Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient’s white blood cell counts are not within normal limits.

5.6 Hematologic Toxicity

In addition to lymphopenia (see Warnings and Precautions (5.3)), decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. Mild to moderate decreases in neutrophil counts (cell count between 1,000 cells per microliter and 7,000 cells per microliter [normal (LLN)] were observed in 27% of MAVENCLAD-treated patients, compared to 13% of placebo patients whereas severe decreases in neutrophil counts (cell count below 1,000 cells per microliter) were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Decreases in hemoglobin levels, in general mild to moderate (hemoglobin...
Liver Injury

In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) considered related to treatment, compared to 0 placebo patients. Onset has ranged from a few weeks to several months after initiation of treatment with MAVENCLAD. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 20-fold the upper limit of normal, have been observed. These abnormalities resolved upon treatment discontinuation.

Obtain complete blood count (CBC) with differential prior to, during, and after treatment with MAVENCLAD [see Dosage and Administration (2.1, 2.5)]. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with MAVENCLAD, as appropriate.

5.7 Liver Injury

In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) considered related to treatment, compared to 0 placebo patients. Onset has ranged from a few weeks to several months after initiation of treatment with MAVENCLAD. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 20-fold the upper limit of normal, have been observed. These abnormalities resolved upon treatment discontinuation.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment courses [see Dosage and Administration (2.1)]. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with MAVENCLAD, as appropriate.

Hypersensitivity

In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD (e.g., dermatitis, pruritus) occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. One patient had a serious hypersensitivity reaction with rash, mucous membrane ulceration, throat swelling, vertigo, diplopia, and headache after the first dose of MAVENCLAD. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine [see Contraindications (4)].

Cardiac Failure

In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately 1 week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

6 Adverse Reactions

The following serious adverse reactions and potential risks are discussed, or discussed in greater detail, in other sections:

- Malignancies [see Warnings and Precautions (5.7)].
- Risk of Transplantogenicity [see Warnings and Precautions (5.2)].
- Lymphopenia [see Warnings and Precautions (5.3)].
- Infections [see Warnings and Precautions (5.4)].
- Hematologic Toxicity [see Warnings and Precautions (5.5)].
- Graft-Versus-Host Disease With Blood Transfusion [see Warnings and Precautions (5.6)].
- Liver Injury [see Warnings and Precautions (5.7)].
- Hypersensitivity [see Warnings and Precautions (5.8)].

6.1 Clinical Trials Experience

Adverse Reactions in Study 1 With an Incidence of at Least 5% for MAVENCLAD and Higher Than Placebo

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7.2 Interferon Beta

Drug Interactions With MAVENCLAD (continued)

Prevention or Management

Concomitant use of MAVENCLAD with interferon beta did not change the exposure of cladribine to a clinically significant extent; however, lymphopenia risk may be increased [see Warnings and Precautions (5.3)].

Prevention or Management

Concomitant use is not recommended.

7.3 Hematotoxic Drugs

Prevention or Management

Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects [see Warnings and Precautions (5.5)].

7.4 Antiviral and Antiretroviral Drugs

Prevention or Management

Monitor hematological parameters.

7.5 Potent ENT, CNT, and BCRP Transporter Inhibitors

Prevention or Management

Avoid concomitant use.

7.6 Potent BCRP and P-gp Transporter Inducers

Prevention or Management

Consider a possible decrease in cladribine efficacy if potent BCRP (e.g., corticosteroids) or P-gp (e.g., rifampicin, St. John’s Wort) transporter inhibitors are co-administered.

7.7 Hormonal Contraceptives

Prevention or Management

It is currently unknown whether MAVENCLAD may reduce the effectiveness of systemically acting hormonal contraceptives.

Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course.
8 Use in Specific Populations

8.1 Pregnancy

Risk Summary
MAVENCLAD is contraindicated in pregnant women and in females of reproductive potential who do not plan to use effective contraception. There are no adequate data on the developmental risk associated with use of MAVENCLAD in pregnant women. Cladribine was embryotoxic when administered to pregnant mice and produced malformations in mice and rabbits (see Data). The observed developmental effects are consistent with the effects of cladribine on DNA (see Contraindications (4) and Warnings and Precautions (5.2)).

Data
Animal Data
When cladribine was administered intravenously (0.05, 1.5, or 3 mg/kg/day) to pregnant mice during the period of organogenesis, fetal growth retardation and malformations (including exencephaly and cleft palate) and embryofetal death were observed at the highest dose tested. An increase in skeletal variations was observed at all but the lowest dose tested. There was no evidence of maternal toxicity.

When cladribine was administered intravenously (0.03, 1, and 3 mg/kg/day) to pregnant rabbits during the period of organogenesis, fetal growth retardation and a high incidence of craniofacial and limb malformations were observed at the highest dose tested, in the absence of maternal toxicity.

When cladribine was administered intravenously (0.05, 1.5, or 3.8 mg/kg/day) to mice throughout pregnancy and lactation, skeletal anomalies and embryolethality were observed at all but the lowest dose tested.

8.2 Lactation

MAVENCLAD is contraindicated in breastfeeding women because of the potential for serious adverse reactions in breastfed infants (see Contraindications (4) and Warnings and Precautions (5.2)). Advise women not to breastfeed during dosing with MAVENCLAD and for 10 days after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

In females of reproductive potential, pregnancy should be excluded before the initiation of each treatment course of MAVENCLAD (see Use in Specific Populations (4.1)).

Contraception

Females

Females of reproductive potential should prevent pregnancy by use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course. It is unknown if MAVENCLAD may reduce the effectiveness of the systemically acting hormonal contraceptives. Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course. Women who become pregnant during MAVENCLAD therapy should discontinue treatment (see Warnings and Precautions (5.2) and Drug Interactions (7.7)).

Males

As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected. Therefore, male patients of reproductive potential should take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)).

8.4 Pediatric Use

The safety and effectiveness in pediatric patients (below 18 years of age) have not been established. Use of MAVENCLAD is not recommended in pediatric patients because of the risk of malignancies (see Warnings and Precautions (5.1)).

8.5 Geriatric Use

Clinical studies with MAVENCLAD did not include sufficient numbers of patients aged 65 or over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic, renal, or cardiac function, concomitant diseases, and other drug therapy.

8.6 Patients With Renal Impairment

The concentration of cladribine is predicted to increase in patients with renal impairment (see Clinical Pharmacology (12.3)). No dosage adjustment is recommended in patients with mild renal impairment (creatinine clearance 60 to 89 mL per minute). MAVENCLAD is not recommended in patients with moderate to severe renal impairment (creatinine clearance below 60 mL per minute) (see Clinical Pharmacology (12.3)).

8.7 Patients With Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown (see Clinical Pharmacology (12.3)). No dosage adjustment is recommended in patients with mild hepatic impairment. MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 6) (see Clinical Pharmacology (12.3)).

17 PATIENT COUNSELING INFORMATION

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

Inform patients of the possible risk of malignancies, teratogenicity, lymphopenia, and other hematologic toxicity, infections, liver injury, hypersensitivity, and cardiac failure. Inform women that they cannot breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose. Instruct patients that MAVENCLAD is a cytoxic drug and to use care when handling MAVENCLAD tablets.
Optimizing the Migraine Consultation

BY MARSHALL C. FREEMAN, MD, FAHS, FAAN, FAANEM

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31 Optimizing the Migraine Consultation

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Critical Need for Optimized Care and Increased Access

IN RECENT YEARS, literature on existing disparities in neurologic care and outcomes has called attention to patient populations facing challenges in both access to care and differences in treatment outcomes. As the field pushes toward the ultimate goal of providing precision medicine to patients, the need to address these challenges becomes increasingly more critical.

A focus on the optimization of patient management approaches has helped ensure that physicians and advanced practice providers can offer the best possible interventions to their patients. In the cover story of this issue of NeurologyLive®, on page 31, Marshall Freeman, MD, dives into the importance of raising the standard for migraine consultation efforts. He explores the approach to these scenarios and offers his insight and expertise as the director of a migraine center to aid in the streamlining of such processes for the patient’s benefit.

Disparities in access to care have been front of mind in the heart of the Bronx, New York, where Montefiore Medical Center has placed an emphasis on improving access to stroke care, particularly for diverse communities. Those living in the cultural melting pot that is the Bronx, where Montefiore’s Stern Stroke Center is located, face myriad obstacles in access to treatment and poststroke support. Our feature story on page 58 highlights the steps the center is taking to connect with the community around it and ensure that patients not only get the care they need but also are well educated on prevention and management.

Keeping with the theme of streamlining care procedures, this issue also features an exploration into hypersomnias. Lauren Chamberlain, DO, and Andrew Spector, MD, offer insight on page 61 on how to properly identify and treat patients with hypersomnia. Additionally, Manolo Bellotto, PhD, offers a look into a novel therapeutic approach to addressing protein misfolding in patients with gene mutation–mediated Parkinson disease, on page 65.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to NeurologyLive®, please email managing editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
COVID-19 infection occurs very frequently, and more studies are needed to better understand the pathophysiology of these headaches and to determine the best treatment options during the period of long COVID-19 syndrome.

All clinicians who seek to “connect the dots” for the right diagnosis and the proper treatment of complex medical issues are recognizing the importance of carefully listening to the patient. A thorough medical history and physical examination provide critical information to neurologists, information that cannot be obtained simply by using modern technology. Collecting excellent history helps us to create an individualized treatment plan based on evidence-based medicine. As neurologists, we study the brain and believe in the powers of the brain. And despite the pandemic, a surge of important new research is emerging, as are new therapeutic developments in our field of medicine.

I am a headache neurologist, and I have found that many patients report “migraine-like” headache, “tension-like” headache, and “trigeminal autonomic cephalalgia-like” headache in different time frames after they have tested positive for COVID-19.

In the International Classification of Headache Disorders, Third Edition (ICHD-3), there is a definition for “headache attributed to systemic viral infection.” There is also the possibility that the cytokine storm–induced inflammation that occurs in many COVID-19 infections could be viewed in the ICHD-3 classifications as “headache attributed to other noninfectious inflammatory intracranial disease.” As the neurological impairments frequently seen in post–COVID-19 patients can have different pathophysiological bases—ranging from direct neurotoxicity to the consequences of hypoxia, hypertension, coagulopathy, and inflammation—multiple physiological factors might be leading to headache during and after the infectious period.

Headache appears to be a heterogenous entity in the setting of COVID-19. Publications vary in their documentation of the percentage of people who report headache during acute COVID-19 infection, with numbers ranging from 14% to 60%, and these numbers might represent an underreporting of headache.

In addition to headache, patients with COVID-19 infections can have other neurologic manifestations. These can be both central nervous system–related (eg, dizziness, cerebrovascular disease, seizure, altered consciousness) or peripheral nervous system–related (eg, neuropathic pain). Skeletal muscular injury has also been reported.

Headache can be one of the prominent symptoms of COVID-19 infection. Results of some studies indicate that it is the most frequent first symptom of COVID-19. In 1 published report, headache persisted after 1 month in 13% of patients. In another study, one-third of followed-up patients had persistent disabling daily headache after 6 weeks, with poor response to acute treatment, and in more than 30% of patients, headache represented the only residual symptom following COVID-19 infection.

In short, a population of patients who have been infected with the virus suffer daily headache without any other symptoms. They may represent a group of new daily persistent headache patients who present at a neurology clinic weeks or even months after their bout with COVID-19, and only with a thorough medical history can it be determined that onset of headache was indeed in a setting of COVID-19 infection.

It has been widely reported that a common symptom of COVID-19 infection is loss of the sense of smell, and a number of studies have examined the possible mechanism for this anosmia. The receptor for the virus, angiotensin converting enzyme-2, is present in the endothelium of blood vessels, including small vessels of the cerebral circulation and the meningeal endothelium. Some data suggest that patients with COVID-19 and headache vs those without headache are more likely to have anosmia.

One reason for loss of smell could be COVID-19–induced olfactory epithelial cell damage. Brain imaging in a patient with COVID-19 and...
an anosmia demonstrated hyperintensity in the gyrus rectus and olfactory bulb areas of the brain. Following viral infection, an inflammatory response in the mucosa of the nose may be likely to occur. Also, activated trigeminal afferents would release calcitonin gene-related peptide. COVID-19 has been shown to activate the trigeminovascular system, and if sensitization of the trigeminovascular system continues, it can lead to persistent headache long after the first positive COVID-19 test. Thus, taken together, all these actions could lead to both headache and suppression of olfactory functions.

We are just beginning to get a better understanding of long COVID syndrome. For example, it has been reported that COVID-19 disease severity might not be a good predictor of the onset of long COVID syndrome. Recognized symptoms of long COVID include fatigue and dyspnea, sleep changes, gastrointestinal (GI) symptoms, and dysautonomia; these can last for months after an acute COVID infection. Other persistent symptoms may include cognitive changes, generalized pain, and cardiac issues.

Among the reported risk factors for long COVID are being female and displaying several specific early symptoms during COVID-19 infection. In addition, some evidence indicates that early dyspnea, prior psychiatric disorders, and specific biomarkers (e.g., D-dimer, C-reactive protein, and lymphocyte count) put a patient at greater risk for developing long COVID. The gut-brain axis change has also been implicated as a potential contributor to the development of long COVID. Persistent gut dysbiosis brought on by COVID-19 infection could negatively modulate neurotransmitter circuits in both the gut and the brain, and it may contribute to the neurologic symptoms of long COVID. This is another excellent example of how neurologists working as team members—in this case, with GI specialists and primary care clinicians—can provide the most helpful care to sufferers of long COVID.

For patients who have been hospitalized with COVID-19 infections, the risk of experiencing residual symptoms can be high. Results of 1 study noted that the median proportion of individuals previously hospitalized with COVID-19 who were experiencing at least 1 persistent symptom after discharge was 72.5%.

Despite an abundance of literature and observations on the presence of headache after COVID-19 infection, not many results about evidence-based treatments have been published on long-COVID headache so far. Some case studies described the use of candesartan, amitriptyline, and onabotulinumtoxinA, which were noted as helpful for some, but not all, patients with long-COVID headache.

Also, some study results indicate that special considerations should be given to people who become infected and who previously presented with migraine. It has been noted that persistent changes in migraine characteristics can occur despite COVID-19 resolution.

The phenotype of headache and comorbidities should be taken into consideration while discussing the pharmacologic treatment for headache after COVID-19 infection. Lifestyle modifications and behavioral therapy should be discussed. Certain procedures that might be helpful include onabotulinumtoxinA injections and nerve blocks. In addition, a trial of neuromodulatory devices could be done. A multidisciplinary team approach is preferred, and advocacy should be in every patient treatment plan. With caregivers and patients working together, we will discover the best way forward.
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease.

An RNAi-based approach that may transform the future for your patients.

Patients and their families face a future of functional decline.

With hereditary transthyretin-mediated (hATTR) amyloidosis...

References:
4. ONPATTRO Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.

Important Safety Information

Infusion-Related Reactions (IRRs)
In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation
ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness).

Adverse Reactions
The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

Please see brief summary of full Prescribing Information following this ad.
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease.

An RNAi-based approach that may transform the future for your patients.

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Study Design

The efficacy of ONPATTRO was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adults with hATTR amyloidosis with polyneuropathy. Patients were randomized to receive ONPATTRO 0.3 mg/kg (N=148) or placebo (N=77) via intravenous infusion once every 3 weeks for 18 months.

Primary endpoint: The modified Neuropathy Impairment Score + 7 (mNIS+7) is an objective 304-point assessment of neuropathy that measures cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology.

Key secondary endpoint: The Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) scale is a patient-reported assessment that evaluates neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy (score range -4 to 136).

Select secondary endpoint: The Composite Autonomic Symptom Score 31 (COMPASS 31) is a patient-reported questionnaire that evaluates 6 autonomic domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor (score range 0 to 100).

At 18 months, ONPATTRO demonstrated:

- **Reversal in neuropathy impairment**: LS mean change from baseline in mNIS+7 of -6.0 points vs 28.0 with placebo, a treatment difference of -34 points (95% CI: -39.9, -28.1; p<0.001)

- **Improvement in quality of life**: LS mean change from baseline in Norfolk QoL-DN score of -6.7 points vs 14.4 with placebo, a treatment difference of -21.1 points (95% CI: -27.2, -15.0; p<0.001)

- **Reduction in autonomic symptoms**: LS mean change from baseline in COMPASS 31 of -5.3 points vs 2.2 with placebo, a treatment difference of -7.5 points (95% CI: -11.9, -3.2; p<0.001)

Visit www.onpattrohcp.com to get your patients started.

CI=confidence interval; LS=least squares; RNAi=ribonucleic acid interference.
ONPATTRO® (patisiran) lipid complex injection, for intravenous use
Initial U.S. Approval: 2018
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

DOSE AND ADMINISTRATION
Dosing Information
ONPATTRO should be administered by a healthcare professional. ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight. For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks. For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

Missed Dose
If a dose is missed, administer ONPATTRO as soon as possible. If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient’s original schedule. If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter.

Required Premedication
All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) [see Warnings and Precautions (5.1) in the full Prescribing Information]. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion: intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent); oral acetaminophen (500 mg); intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent); and intravenous H1 blocker (e.g., ranitidine 50 mg, or equivalent).

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs [see Warnings and Precautions (5.1) in the full Prescribing Information].

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs resulted in permanent discontinuation in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies.

Across clinical studies, the most common adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs [see Warnings and Precautions (5.1) in the full Prescribing Information].

Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion [see Dosage and Administration (2.2) in the full Prescribing Information]. Monitor patients during the infusion for signs and symptoms of IRRs. Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, diziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

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

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidoses (HATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 186 patients exposed for at least 1 year, 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 11.7 months).

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Table 1 lists the adverse reactions that occurred in at least 5% of patients in the ONPATTRO-treated group and that occurred at least 3% more frequently than in the placebo-treated group in the randomized controlled clinical trial.

Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-Treated Patients and at Least 3% More Frequently in Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONPATTRO N=148</th>
<th>Placebo N=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections a</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Infusion-related reaction b</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea c,d</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vertigo</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

aIncludes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.

bInfusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, diziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

cNot part of an infusion-related reaction.

dIncludes dyspepsia and exertional dysnea.

Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Ocular adverse reactions that occurred in 5% or less of ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Two serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Extravasation was observed in less than 0.5% of infusions in clinical studies, including cases that were reported as serious. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ONPATTRO.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Recommended Supplementation
Recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).
ONPATTRO® (patisiran) lipid complex injection, for intravenous use

Symptoms of infusion-related reactions have included syncope [see Warnings and Precautions (5.1)] and pruritus.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-877-256-9526 or by contacting alnylampsregnancyprogram@iqvia.com.

**Risk Summary**

There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetuses of a reduction in maternal serum TTR caused by ONPATTRO and of vitamin A supplementation are unknown [see Clinical Pharmacology (12.2), Warnings and Precautions (5.2) in the full Prescribing Information].

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats [see Data in the full Prescribing Information]. 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**

Intravenous administration of patisiran-LC (0, 0.35, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (15 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis resulted in no adverse effects on embryofetal development. In a separate study, patisiran-LC (0, 0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.3, 0.5, or 1.5 mg/kg) or a rodent-specific surrogate (15 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

**Lactation**

**Risk Summary**

There is no information regarding the presence of ONPATTRO 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 ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG3900–C-DMOG) were present in milk.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

No dose adjustment is required in patients ≥65 years old [see Clinical Pharmacology (12.3) in the full Prescribing Information]. A total of 62 patients ≥65 years of age, including 9 patients ≥75 years of age, received ONPATTRO in the placebo-controlled study. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Impairment**

No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤1 x ULN and AST ≤1 x ULN, or bilirubin >1.0 to 1.5 x ULN) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

**Renal Impairment**

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73m²) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

**PATIENT COUNSELING INFORMATION**

**Infusion-Related Reactions**

Inform patients about the signs and symptoms of infusion-related reactions (e.g., flushing, dyspnea, chest pain, syncope, rash, increased heart rate, facial edema). Advise patients to contact their healthcare provider immediately if they experience signs and symptoms of infusion-related reactions [see Warnings and Precautions (5.1) in the full Prescribing Information].

**Recommended Vitamin A Supplementation**

Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [see Warnings and Precautions (5.2) in the full Prescribing Information].

**Pregnancy**

Instruct patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO [see Use in Specific Populations (8.1) in the full Prescribing Information].

Manufactured for: Alnylam Pharmaceuticals, Inc.
300 Third Street, Cambridge, MA 02142
By: Ajinomoto Althea, Inc.
11040 Roselle Street, San Diego, CA 92121
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TTR02-USA-01517-V2
FDA Approves New Option for Pediatric Epilepsy

By Marco Meglio

For the first time in 7 years, the FDA has approved an IV agent for pediatric patients with partial-onset seizures.

The expanded indication for brivaracetam (Briviact; UCB Pharma) CV tablets and oral solution also includes an IV formulation for when oral administration is temporarily not feasible.1

Brivaracetam, a third-generation antiepileptic racetam derivative and a 4-n-propyl analogue of levetiracetam (Keppra; UCB Pharma), is now approved as both monotherapy or adjunctive therapy and is administered in tablets, an oral solution, and an IV dosage. The basis for the approval stems from long-term data that showed high retention rates of the therapy across a 2-year stretch. In an open-label follow-up study that included 168 pediatric patients with partial-onset seizures, 71.4% and 64.3% of patients remained on treatment at 1 and 2 years, respectively.1

UCB’s agent received approval from the FDA in 2016 as an add-on therapy for adults and was then approved as a monotherapy for adults in September 2017. It received an expanded indication in 2018 as an adjunctive therapy for patients 4 years and older with partial-onset seizures.

Brivaracetam has demonstrated a well-tolerated safety profile that has been similar in both pediatric and adult studies. The most commonly observed adverse events (AEs) reported in adults were somnolence and sedation, dizziness, fatigue, and nausea and vomiting.2

A phase 2a, open-label, single-arm, fixed 3-step dose-escalation trial (NCT00422422) published in 2019 provided preliminary information that short-term adjunctive brivaracetam treatment is well tolerated in children aged 1 month to 16 years old with epilepsy.3 In that study, 90% of the 100 patients enrolled completed the trial, with treatment-emergent AEs reported by 32.3 (32 of 99) patients. Responder rates of at least 50% were 21.3% (all patients; n = 80) and 26.4% (patients with focal seizures, aged 4 to < 16 years; n = 22).

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

Novel Reformulation of Acute Migraine Treatment Gets Green Light

By Marco Meglio

Impel NeuroPharma’s INP104 nasal spray for the acute treatment of migraine headaches with or without aura in adults has received FDA approval. Marketed as Trudhesa, it utilizes the company’s Precision Olfactory Delivery technology, a novel delivery system that targets the upper nasal space.1

INP104’s intranasal administration is designed to attempt to optimize the delivery of dihydroergotamine mesylate (DHE) for fast relief regardless of the time since migraine onset. According to Impel, the system is also designed to deliver a lower dose of DHE compared with other nasally administered, FDA-approved products, which reduces the adverse effects (AEs) that are typically associated with delivery of DHE to the lower nasal space.

The FDA’s decision was based on data from the phase 3 STOP 301 study (NCT03557333), in which INP104 met the primary end point and demonstrated no new safety signals or concerning trends during the 52-week study period. The data were included in Impel’s new drug application, which was filed in November 2020 and accepted in January of this year.2

Overall, 74% and 90% of patients completed the 24- and 52-week phases of the study, respectively. Efficacy data in the full safety set (FSS) showed that 66.3% of patients experienced pain relief with treatment. Furthermore, 38% of the group reported pain freedom and 52% had freedom from their most bothersome symptom (MBS) 2 hours after their first dose of INP104.

In the 24-week FSS, most treatment-emergent AEs (TEAEs) were mild and transient. The most frequently reported TEAEs (≥ 5%) during the period were nasal congestion (16.7%), nausea (7.9%), nasal discomfort (5.4%), and abnormal taste (5.1%). Notably, investigators did not observe any cardiac TEAEs or significant changes in mean heart rate. No serious AEs were recorded over the 52-week period.

Open-label results from STOP 301 were presented at the 2021 American Headache Society 63rd Annual Scientific Meeting held June 3 to 6. Data presented showed that INP104 was associated with improvements in several migraine measures, low recurrence rates, and consistent efficacy over 24 weeks.2,5

The mean number of migraine attacks (MAs) self-reported as pain and MBS free 2 hours post INP104 dosing ranged from 35.1% to 38.7% and 49.2% to 57.9% compared with 30.6% and 47.9% at baseline, respectively. At 52 weeks, the mean number of MAs self-reported as pain and MBS free 2 hours post INP104 ranged from 31.4% to 39% and 39.8% to 55.7% compared with 23.5% and 40.8% at baseline, respectively. In total, 15% of MAs required a rescue medication over the 24-week period; 90.9% of patients opted to use non-INP104 medications in lieu of the second optional dose, which was allowed within 24 hours.3

INP104 also demonstrated a significant consistency of response. Over 24 weeks, 25%, 57%, and 59.9% of patients were 100%, 75% or greater, and 67% or greater responders, respectively. After 24 weeks, 22.2%, 58.3%, and 65.3% of patients were 100%, 75% or greater, and 67% or greater responders, respectively.3

Treatment consistency was observed in a separate analysis that included 188 patients in the 24-week FSS who had 4 or more INP104-treated MAs in both weeks 1 to 12 and 13 to 24. Within-person consistency in 2-hour headache response was defined as the proportion of treated MAs (100%, ≥ 75%, and ≥ 67%) having mild or no pain at 2 hours post INP104.

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

Idiopathic Hypersomnia Receives Coveted First Approval

By Marco Meglio

The FDA has approved the first treatment for idiopathic hypersomnia. JZP-258 (marketed as Xywav), a combination agent of calcium, magnesium, potassium, and sodium oxybates, will be available to patients in the fourth quarter of 2021 following Risk Evaluation and Mitigation Strategies implementation.1

Jazz Pharmaceuticals announced in February the acceptance of its supplemental new drug application for JZP-258, which included data from...
a positive phase 3 study (NCT03533114) that showed the investigational agent was effective and safe for adults with idiopathic hypersomnia. The oral solution received fast track designation from the FDA in September 2020 for this indication and was granted a rolling submission that December, allowing for the submission of portions of the application as completed.

Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by chronic excessive daytime sleepiness (EDS). A majority of physicians in the space have turned to off-label use of wake-promoting therapies typically used in patients with narcolepsy to help address the sleepiness issues.

The double-blind, multicenter, randomized phase 3 trial featured patients who had EDS associated with idiopathic hypersomnia, and all those treated with the agent experienced clinically meaningful improvements in Epworth Sleepiness Scale (ESS) scores—the primary end point—during the open-label titration period.

A randomized withdrawal portion of the study included 115 patients who were assessed on primary and key secondary end points including Patient Global Impression of Change (PGIC) and Idiopathic Hypersomnia Severity Scale (IHSS). Those who received JZP-258 reported clinically meaningful maintenance of efficacy as measured by all 3 evaluations. Furthermore, highly statistically significant worsening was observed for those who received placebo compared with JZP-258 for ESS (P < .0001), PGIC (P < .0001), and IHSS (P < .0001).

JZP-258 has a boxed warning as a central nervous system depressant and for its potential for abuse and misuse. The most common adverse reactions, occurring in at least 5% of adults in the phase 3 study, were nausea, headache, dizziness, anxiety, insomnia, decreased appetite, hyperhidrosis, vomiting, diarrhea, dry mouth, parasomnia, somnolence, fatigue, and tremor.

JZP-258 originally received approval for the treatment of cataplexy or EDS in patients 7 years or older with narcolepsy in July 2020. The basis of that approval was built on data from a phase 3 double-blind, placebo-controlled, randomized-withdrawal, multicenter study, for which the drug demonstrated statistically significant differences (P < .0001) in the weekly number of cataplexy attacks and ESS scores compared with placebo.

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

## JOURNAL RUNDUP

### Epilepsy Agent Displays High Real-world Retention Rates, Consistent Safety

Results from the PERMIT study, a pooled analysis of 44 real-world studies, demonstrated that perampanel (Fycompa; Eisai) is effective and generally well tolerated in patients with focal or generalized epilepsy. With more than 5000 patients with epilepsy (PWE) included in the cohort, PERMIT remains the largest pooled analysis of perampanel clinical practice data to date.1

Investigators assessed outcomes such as retention, effectiveness, 50% responder rate, seizure freedom rate, and rates of worsened seizure frequency among a cohort of 5193 PWE treated with perampanel. Safety and tolerability information, evaluated by number and types of adverse events (AEs), was also included, as well as AEs leading to discontinuation, psychiatric AEs, and psychiatric AEs leading to discontinuation.

Perampanel showed profound retention rates across a 1-year stretch. At 3, 6, and 12 months, the retention rates were 90.5%, 79.8%, and 64.2%, respectively. Additionally, the mean retention time on perampanel was 10.8 months (95% CI, 10.6-10.9), and 14.3% (600 of 4201) of patients discontinued over the 12-month period because of AEs. Lack of efficacy (8.8%; 368 of 4201), both AE and lack of efficacy (3.3%; 139 of 4201), seizure worsening (1.2%; 49 of 4201), other (0.8%; 34 of 4201), and unknown (7.5%; 313 of 4201) rounded out other reasons for perampanel discontinuation. A total of 29.5% (1229 of 4164) of patients retained treatment for longer than the prespecified 12-month period.

Among 1896 PWE, 96.3% (n = 1825) presented having had at least 1 seizure in the past 3 months. At the last visit, investigators observed a monthly seizure frequency of 0.7 (mean, 7.3 [SD, 22.2]; range, 0-300) compared with 3.0 (mean, 17.2 [SD, 60.6]; range, 0.1-1120.0) at baseline. These data correlated to a 57.3% mean reduction from baseline (median, 75%). Notably, the percentage of individuals with focal seizures decreased significantly, from 71.8% at baseline to 51.9% at the last visit (McNemar test; P < .001).

There were also significant decreases in the frequency and proportions of PWE with focal aware seizures, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures. Additionally, the percentages of PWE with primary generalized seizures, primary generalized tonic-clonic seizures, absence seizures, and myoclonic seizures were all shown to have decreased at final visit.

Responder rate, where response was defined as seizures under control, was 58.3% vs 50.0% at the 12-month and final visit periods, respectively. At the same time, seizure freedom rate was 23.2% vs 20.5%, with 195 PWE presenting with no seizures at every recorded time point during follow-up. Among a subgroup of 74 PWE with status epilepticus, 52.7% (n = 39) responded to perampanel treatment.

Worsened seizure frequency was generally stable at all time points of the study, with 6.6% and 10.1% of patients experiencing worsened seizure frequency at 12 months and last visit, respectively. Among those with focal seizures, the worsened seizure frequency was 7.6% at 12 months and 11.2% at the last visit.

Overall, 49.9% of the cohort reported experiencing AEs at some point during follow-up, the most frequent being dizziness/vertigo (15.2%). Other commonly reported AEs included somnolence (10.6%), irritability (8.4%), behavioral disorders (5.4%), instability/ataxia (4.1%), and fatigue (3.7%). Notably, those who used fast perampanel titration had significantly higher incidence of AEs compared with those for whom a slow transition was used (61.9% [646 of 1043] vs 46.4% [295 of 636]; X² = 9.36; P = .002).

In total, 21% of the cohort experienced psychiatric AEs. Additionally, investigators observed a significant association between these AEs and the presence of previous psychiatric comorbidity (X² = 52.43; P < .001). The most frequent psychiatric AEs in those who discontinued treatment because of AEs were irritability (3.1%), behavioral disorders (2.8%), and mood disturbances (1.1%). No cases of homicidal ideation were reported.

For a full list of references, see the article on NeurologyLive.com.
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SCRXT: We caught up with @neurology_live at AAIC21 to delve into the compelling evidence supporting P. gingivalis’ role in Alzheimer’s pathologies as top-line data from our pivotal disease-modifying GAIN study approaches in mid-November 2021.
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In a conversation with @neurology_live, AASM President Raman Malhotra, MD, commented on the importance of sleep for patients in hospitals and long-term care facilities. @malhotra_md.
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@neurology_live Thank you for reporting on research presented at AAIC2021 which found that long-term, daily treatment with non-invasive stimulation was both safe and well-tolerated in people living with Alzheimer’s disease.
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NEUROLOGYLIVE VIDEOS

STUDYING HEADACHE IN TRANSGENDER AND GENDER-DIVERSE PATIENTS
Jennifer Hranilovich, MD, assistant professor of pediatrics and neurology, University of Colorado School of Medicine, spoke on a narrative review investigating headache in gender minorities, a population in great need of additional research and care assessment.
+ VIEW VIDEO neurologylive.com/hranilovich

COVID-19’S POTENTIAL EFFECT ON DEMENTIA RISK
James E. Galvin, MD, MPH, director, Comprehensive Center for Brain Health, University of Miami Miller School of Medicine, discussed COVID-19 and Alzheimer disease, including what the clinical community should know.
+ VIEW VIDEO neurologylive.com/galvin

IS TELEHEALTH HERE TO STAY FOR ALZHEIMER DISEASE CARE?
Jessica L. Zwerling, MD, MS, director, Montefiore Hudson Valley Center of Excellence for Alzheimer’s Disease, shared her experience with telemedicine in Alzheimer disease over the past year and how it can increase access, help overcome social determinants of health, and encourage engagement with the community.
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INCORPORATING PHYSICAL THERAPY INTO MS CARE
Patricia Bobryk, MHS, PT, MSCS, ATP, physical therapist, UC Health, and co-chair, International Organization of Multiple Sclerosis (MS) Rehabilitation Therapists, shared her insight into the clinical care of MS from the perspective of a rehabilitative specialist, and including physical therapy in multidisciplinary care.
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16 Vol. 4 | No. 5 | October 2021 NeurologyLive.com
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INDICATION
KESIMPTA 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
Contraindication: KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

WARNINGS AND PRECAUTIONS
Infections: An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti-CD20 antibodies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

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

Make KESIMPTA your 1st choice for RMS

POWER
In two Phase 3 pivotal clinical trials vs teriflunomide, KESIMPTA demonstrated:
- Significant reduction in ARR of up to nearly 60% vs teriflunomide (P<0.001)\(^1\)\(^2\)
- Profound reduction in mean number of Gd+ T1 lesions per scan of up to 98% (P<0.001)\(^1\)
- Superior reduction in mean number of new or enlarging T2 lesions per year of up to 85% (P<0.001)\(^1\)
- Significant risk reduction in 3-month CDP of 34% (P=0.002) and 6-month CDP of 32% (P=0.01)\(^1\)\(^2\)

PRECISION
- A targeted and precisely delivered B-cell therapy\(^3\)\(^4\)

Safety
- Favorable safety profile similar to teriflunomide as demonstrated in 2 pivotal trials\(^1\)

FLEXIBILITY
- The first once-monthly (20 mg), SC, B-cell therapy administered at home or anywhere\(^5\)\(^6\)

Learn more at KesimptaHCP.com

Study Design: ASCLEPIOS I and II were 2 identical randomized, active-controlled, double-blind Phase 3 studies in patients with RMS, approximately 40% of whom were DMT treatment naïve. Patients were randomized to double-dummy subcutaneous KESIMPTA (20 mg every 4 weeks) or oral teriflunomide (14 mg daily) for up to 30 months. Primary endpoint was ARR. Key MRI endpoints were number of Gd+ T1 lesions, and annualized rate of new or enlarging T2 lesions. A key clinical endpoint was reduction in risk of 3-month CDP. Treatment duration was variable based on end of study criteria. Maximum duration 120 weeks, median duration 85 weeks.
ARR=annualized relapse rate; CDP=confirmed disability progression; DMT=disease-modifying therapy; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis; SC=subcutaneous.
*Primary endpoint: relative reduction in adjusted ARR vs teriflunomide of 51% (0.11 vs 0.22) in ASCLEPIOS I and 59% (0.10 vs 0.25) in ASCLEPIOS II.
\(^1\)Key clinical and MRI endpoints: reduction in mean number of Gd+ T1 lesions per scan vs teriflunomide of 98% (0.01 vs 0.45 ) in ASCLEPIOS I and 94% (0.03 vs 0.51) in ASCLEPIOS II; reductions in T2 lesions vs teriflunomide of 82% (0.72 vs 4.00) in ASCLEPIOS I and 85% (0.64 vs 4.15) in ASCLEPIOS II; reduced risk in 3-month CDP vs teriflunomide of 34% (15.0 vs 10.9) and 6-month CDP of 32% (8.1 vs 12.0) in pooled populations from both trials.
\(^1\)The initial dose period consists of 20 mg SC doses at Weeks 0, 1, and 2.
\(^1\)KESIMPTA Sensoready\®" Pens must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake.
IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Hepatitis B Virus: Reactivation: No reports of hepatitis B virus (HBV) reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy. For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

Injection-Related Reactions: Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

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

KESIMPTA, the KESIMPTA logo, and SENSOREADY are registered trademarks of Novartis AG.
Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain. Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional. If injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7% of patients treated with KESIMPTA compared to 3.1% of patients treated with teriflunomide in RMS clinical trials [see Adverse Reactions (6.1)]. Treatment was discontinued because of decreased immunoglobulins in 3.4% of patients treated with KESIMPTA and in 0.8% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Fetal Risk

Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-COD2 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections [see Warnings and Precautions (5.1)]
- Injection-Related Reactions [see Warnings and Precautions (5.2)]
- Reduction in Immunoglobulins [see Warnings and Precautions (5.3)]

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 clinical practice. Approximately 1500 patients with RMS received KESIMPTA in clinical studies. In Study 1 and Study 2, 1682 patients with RMS were randomized, 946 of whom were treated with KESIMPTA for a median duration of 85 weeks; 33% of patients receiving KESIMPTA were treated for up to 120 weeks [see Clinical Studies (14.1) in the full prescribing information]. The most common adverse reactions occurring in greater than 10% of patients treated with KESIMPTA and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The most common cause of discontinuation in patients treated with KESIMPTA was low immunoglobulin M (3.3%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

### Table 1: Adverse Reactions in Patients with RMS with an Incidence of at least 5% with KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>KESIMPTA 20 mg</th>
<th>Teriflunomide 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections*</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Injection-related reactions (systemic)</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Injection-site reactions (local)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Blood immunoglobulin M decreased</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinuses, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

Injection-Related Reactions and Injection-Site Reactions

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4%), decreasing with subsequent injections (4.4% with second, less than 2% with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with KESIMPTA reported serious injection-related reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue. In addition to systemic injection-related reactions, local reactions at the administration site were very common. Local injection-site reactions were all mild to moderate in severity. The most frequently reported symptoms (2% or greater) included erythema, pain, itching, and swelling [see Warnings and Precautions (5.2)].
Laboratory Abnormalities

Immunoglobulins

In Study 1 and Study 2, a decrease in the mean level of IgM was observed in KESIMPTA-treated patients but was not associated with an increased risk of infections [see Warnings and Precautions (5.3)]. In 14.3% of patients in Study 1 and Study 2, treatment with KESIMPTA resulted in a decrease in a serum IgM that reached a value below 0.34 g/dL. KESIMPTA was associated with a decrease of 4.3% in mean IgG levels after 48 weeks of treatment and an increase of 2.2% after 96 weeks.

6.2 Immunogenicity

As with all therapeutic proteins, 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 medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) KESIMPTA-treated patients; no patients with treatment enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of KESIMPTA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with KESIMPTA.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating KESIMPTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies (see Data).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA in utero until B-cell recovery occurs [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2) in the full prescribing information].

Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans (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.

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of KESIMPTA did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

Data

Animal Data

Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestations days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (Cave) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (Cave) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose. The deaths at the high dose were considered secondary to B-cell depletion. Plasma exposure (Cave) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose.

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Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

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T2020-112
Brisk Walking Exercise Improves Nonmotor Parkinson Disease Symptoms

By Matt Hoffman

DATA FROM A PROSPECTIVE, 2-arm, 6-week, single-blinded, randomized, controlled trial suggest that a brisk walking program may alleviate the nonmotor symptoms experienced by patients with Parkinson disease (PD).1

The group randomized to the experimental program (n = 32) experienced a significant increase in their Movement Disorder Society–Unified Parkinson’s Disease Rating Scale nonmotor (MDS-UPDRS-I) scores, for a mean reduction of 2.4 points (±0.4; \( P < .001 \)) compared with the control group (n = 32). The group-by-time interaction was also significant (\( P < .05 \)).

Additionally, Pittsburgh Sleep Quality Index (PSQI) and Parkinson Disease Questionnaire-39 summary index (PDQ-39 SI) scores had nonsignificant reduction, by 1.6 and 1.2 points, respectively, compared with the control group (n = 32). No adverse effects were reported during the training period.1

These data were presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress 2021, September 17-22, by Margaret Mak, PhD, Shun Hing Education and Charity Fund Professor in Rehabilitation Sciences, associate dean, Faculty of Health and Social Sciences, and professor of rehabilitation sciences, Hong Kong Polytechnic University. This work was conducted as a follow-up to the group’s prior pilot study of the program.

“Brisk walking is a moderate-intensity aerobic training that involves good coordination of large steps and large arm swing,” Mak said in her presentation, adding that “Our previous pilot study’s results indicated that the 6-week brisk walking program also increased in motor performance, balance, and walking capacity among people with mild to moderate PD; however, the effects of brisk walking on nonmotor symptoms, sleep quality, and health-related quality of life [had] not been investigated.”

Mak told NeurologyLive® that she believes this type of program could be easily implemented and tailored for patients in clinical practice, particularly noting that this can be achieved without additional exercise equipment. “The use of a smartwatch to give feedback to [patients] about goal attainment encourages them to continue training. It requires a low level of manpower and resources, just a weekly group training supervised by physiotherapists, with tapered supervision after 6 weeks,” she explained.

“Group training can provide mutual support and tapered supervision can empower and motivate [patients] for good exercise compliance,” Mak added.

The 64 total patients in the trial were randomized to the 2 aforementioned groups after a baseline assessment. All participants attended six 90-minute weekly sessions under physiotherapy supervision. Those in the experimental group underwent a group brisk walking exercise regimen tracked with a smartwatch, the data from which were accessible via an online portal. The regimen featured some consistent warm-up and cool-down tasks, with training increasing after certain times.

The control group, on the other hand, practiced upper limb stretching and strengthening, as well as dexterity training while sitting. Their regimen consisted of 20-minute warm-up and cool-down exercises plus 50 minutes of upper limb, lower limb, and trunk stretches, followed by TheraBand upper limb strengthening for 15 minutes.

Although Mak and colleagues noted that the brisk walking program appears to alleviate nonmotor symptoms of PD after 6 weeks.
post-training, she added in her presentation that “further study is important to investigate the long-term effects of this program.”

“We have recruited more patients and are collecting more data on the 6-month training effect and the carryover effect after treatment completion to examine whether this training can be sustained after treatment ended. In the future study, we can include other nonmotor outcomes such as fatigue and mood, as well as motor outcomes such as MDS-UPDRS scores,” Mak told NeurologyLive®.

This is not the first work to suggest that aerobic exercise can benefit patients with PD. Data published in 2019 in The Lancet Neurology by van der Kolk et al. suggest that those with mild PD can benefit from a high-intensity aerobic exercise intervention, when gamified and delivered in an at-home fashion, specifically attenuating disease symptoms. That single-center assessment, called Park-in-Shape, included 130 patients randomized to either the aerobic intervention (n = 65) or active control (n = 65) group and followed for 6 months.1

Park-in-Shape’s aerobic exercise included cycling on a stationary home-trainer for 30 to 45 minutes thrice weekly, compared with a nonaerobic regimen of stretching, flexibility, and relaxation exercises for 30 minutes thrice weekly. Ultimately, the aerobic group reported significantly improved OFF state MDS-UPDRS motor section scores compared with the control group, differing by 4.2 points (95% CI, 1.6-6.9; P = .0020).

RESULTS FROM THE OPEN-LABEL, nonrandomized, phase 2b BeyonND study (NCT02726386) demonstrated that treatment with ND0612 (NeuroDerm), an investigational subcutaneous levodopa/carbidopa delivery system, increased good ON time while reducing OFF time and motor disability in patients with Parkinson disease (PD) and motor fluctuations.1

The results, presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress 2021, September 17-22, showed that the agent improved good ON time by an adjusted mean of 2.3 hours at month 3 in the 24-hour dosing regimen (n = 44) and 2.6 hours in the 16-hour dosing regimen (n = 83). The improvements were maintained over the 12-month study period. Presenting author Ryan Case, PhD, head, Clinical Medical Affairs, NeuroDerm, and colleagues, wrote that "these results are above those achieved with oral adjunct therapies and well above the 1-hour change that is considered clinically relevant."

The investigators evaluated the long-term safety and efficacy of a duo of ND0612 dosing regimens in patients with PD who had Hoehn & Yahr scores of at least 3 during ON time and experienced at least 2 hours of daily OFF time. In addition to evaluating ON time and OFF time, investigators assessed activities of daily living (ADL) and motor through the Unified Parkinson’s Disease Rating Scale (UPDRS) score.

At month 3, those in the 24-hour regimen group experienced decreases in OFF time by an adjusted mean of 2.3 hours while those in the 16-hour dosing regimen experienced similar OFF time decreases of 2.4 hours. Both reductions were sustained over 12 months. Both treatment regimen groups showed improvements in UPDRS-motor scores that began within the first month and were maintained through month 12 (24-hour regimen: month 1 least square [LS] mean change from baseline, –6.62 [95% CI, –8.56 to –4.67]; month 12, –6.09 [95% CI, –8.61 to –3.57]; 16-hour regimen: month 1, –6.61 [95% CI, –8.30 to –4.91]; month 12, –5.12 [95% CI, –7.37 to –2.87]).

Patients in the 24-hour regimen group had improvements of –3.06 (95% CI, –3.92 to –2.20) and –2.47 (95% CI, –3.75 to –1.19) in UPDRS ADL scores at months 1 and 12, respectively. Those in the 16-hour regimen group experienced similar results, with improvements of –3.68 (95% CI, –4.43 to –2.93) at month 1 and –2.49 (95% CI, –3.62 to –1.36) at month 12.

ND0612 is also currently being assessed in a phase 3, multicenter, double-blind, parallel-group, randomized trial (NCT04006210) called BouNDless. Announced in 2019, the study is evaluating 300 patients in 2 groups, randomized to either the infusion of ND0612 plus placebo carbidopa/levodopa and active carbidopa/levodopa tablets 25 mg/100 mg, or a placebo comparator.2

In previous phase 2 studies, the investigational therapy was shown to maintain consistent, therapeutic levodopa plasma concentrations associated with major changes in clinical parameters, including OFF-time reduction, when added to optimal oral standard of care. OFF time was reduced by 2 hours, or 41%, in the treatment group (n = 18) compared with 9% in the placebo group (n = 11). Overall, the global clinical improvement in disease severity for the treatment group was 90%, compared with 36% for placebo, and quality of life was improved by 17%, compared with 5%, respectively.3

As well, preliminary data from a phase 2a trial (NCT02577523) of ND0612H were presented at the 2017 MDS Congress. It enrolled 38 patients who received either 24-hour or 14-hour infusions for 28 days and showed that off time was significantly reduced. All told, off time dropped from 5.5 hours per day to 2.8 hours, and on time increased from 11% to 50% after 28 days. By 9 AM, three-quarters of patients experienced symptom relief.4

ND0612 Subcutaneous Levodopa Delivery System Demonstrates Efficacy in Phase 2 Setting

By Marco Meglio

For a full list of references, see the article on NeurologyLive.com.
Opicapone Demonstrates Small Benefit for Sleep in Parkinson Disease

By Marco Meglio

A POOLED ANALYSIS OF PATIENTS WITH Parkinson disease (PD) from the BIPARK I and II studies (NCT015668073; NCT91227655) revealed a modest positive benefit for sleep when treated with opicapone (Ogentys; Neurocrine Bio) 50 mg once daily as an add-on to current levodopa/carbidopa regimen, although the data was limited by small sample sizes. The findings were presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress 2021, September 17-22, by Robert A. Hauser, MD, director, Parkinson’s Disease and Movement Disorders Center, University of South Florida.

Investigators assessed the effects of opicapone, a selective catechol-O-methyltransferase inhibitor, in a pooled population of individuals with PD who had at least 1 awakening after falling asleep, based on 24-hour patient diaries. These post hoc analyses evaluated outcomes such as number of times that participants awake after sleep onset in an OFF episode, total awake time after sleep onset (WASO), and percent of sleep time spent awake.

The data set included 522 patients (opicapone, n = 265; placebo, n = 257) with PD with motor fluctuations. These patients had mean motor fluctuation duration of over 2.5 years and a mean daily OFF time over 6 hours. Among the total cohort, 14.8% (opicapone, 18.9%; placebo, 27.0%) woke up after sleep onset and 79.2% (61 of 77) of these participants woke up in an OFF episode.

Although the effects were modest, there was a decreased frequency of awakenings at week 14/15, or the conclusion of the study, in those treated with opicapone, but not in those who received placebo (mean change from baseline: opicapone, –0.9; placebo, 0.1). Additional modest improvements were observed for opicapone, but not placebo, on percent of participants who were awake (WASO duration: opicapone, –0.5; placebo, 2.0%). Hauser and colleagues concluded that “more research is needed to better understand the effects of opicapone on sleep in patients with PD who are experiencing motor fluctuations.”

In April 2020, opicapone received FDA approval as a once-daily adjunctive treatment of OFF episodes in patients with PD. The US approval was supported by 38 clinical studies of more than 1000 patients, and included both phase 3 BIPARK studies.

Results of BIPARK-1 revealed a placebo-adjusted OFF time reduction of 60.8 minutes in the 50-mg group, a 51% reduction that was observed in the active comparator group (40.3 minutes). BIPARK-2 included 427 patients with PD and motor fluctuations and showed that treatment with 50-mg opicapone had a significant 54.3-minute reduction in OFF time vs placebo, with daily OFF time reduced by 126.3 minutes over 1-year follow-up.

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

Prasinezumab Shows Potential Effect of Delaying Motor Progression in Parkinson Disease

By Marco Meglio

TREATMENT WITH PRASINEZUMAB (ROCHE), an investigational humanized monoclonal antibody previously known as PRX002, resulted in slight delay of motor progression, leading to more favorable trajectories in patients with Parkinson disease (PD). Investigators noted that this signal of change needs to be confirmed with additional studies.

These results were from part 2 of the phase 2 PASADENA study (NCT03100149) and were presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress 2021, September 17-22, by Gennaro Pagano, MD, MSc, PhD, expert medical director, Roche. Overall, 316 participants were recruited in the study, 309 of whom started part 2 and were included in the analysis. Patients included in the study had diagnosis of early PD, were drug-naïve or treated with monoamine oxidase B inhibitors.

Pagano and colleagues evaluated the efficacy of prasinezumab in an exploratory delayed-start analysis in individuals with early PD following 104 weeks of double-blind treatment. The humanized antibody is designed to bind to aggregated α-synuclein with higher selectivity over monomeric α-synuclein. By clearing α-synuclein clumps, the agent is thought to slow neurodegeneration associated with the protein’s toxic accumulation and its transmission to neighboring neurons.

Patients were randomized 1:1:1 to receive intravenous prasinezumab every 4 weeks (low dose [1500 mg] or high dose [3500 mg for body
CONFERENCE HIGHLIGHTS

Home Health DBS Management Proves Feasible for Parkinson Disease

By Matt Hoffman

OPEN-LABEL, RANDOMIZED CLINICAL TRIAL DATA presented at the International Parkinson and Movement Disorders Society (MDS) Virtual Congress 2021, September 17-22, suggest that conducting home health management via deep brain stimulation (DBS) postoperatively is safe and feasible for patients with Parkinson disease (PD).1

All told, the primary outcome—defined as the number of times each patient traveled to the movement disorders clinic during the study period—revealed that those randomized to home health management (n = 23; 0.4 visits ±0.8) had fewer clinic visits than those who were in the standard-of-care arm (SOC, n = 21; 4.8 visits ±0.4), a significant between-group difference (P < .0001).

“The travel required to receive [DBS] programming is a substantial burden on patients, and limits those who can access DBS therapy,” the authors, including Adolfo Ramirez-Zamora, MD, associate professor, program director, and chief, Division of Movement Disorders, University of Florida, wrote.

Ramirez-Zamora et al observed no significant differences between the groups in the secondary outcomes measuring the efficacy of DBS, which included changes from baseline in the Unified Parkinson’s Disease Rating Scale part III (UPDRS III). No adverse events (AEs) were deemed related to the study procedure or devices.

The final analyses included 19 patients in the SOC group and 23 patients in the home health who underwent a minimum of 1 postoperative management visit. The home health postoperative management included 2 in-person visits and 3 phone-based visits, conducted by a home health nurse who chose DBS settings with the aid of an iPad-based mobile application for PD DBS system. Before the study period, the home health nurse had no experience providing DBS care.

The study was conducted at University of Florida Health from 2017 to 2020, with consenting participants who were receiving DBS as part of SOC treatment for PD were 1:1 randomized to receive either SOC or home health postoperative DBS management for the first 6 months after surgery. Primary caregivers, usually the spouse, were also enrolled to assess caregiver strain.

Although DBS has established itself as an effective approach in PD care, because of the need for surgical procedures to utilize it, many patients who are candidates are hesitant to undergo such operations. Data have shown that surgical care for PD is safe and effective, and many physicians say it should no longer be a consideration of last resort, particularly in light of the innovations in neurobiology, science, technology, engineering, and public awareness that are shaping the future of DBS.

One of those innovations has been the development of adaptive DBS, an investigational feature of the Percept PC device that uses proprietary BrainSense technology to continuously capture and record brain signals while delivering therapy. In January, Medtronic announced ADAPT-PD trial (NCT04547712) to evaluate the safety and efficacy of adaptive deep brain stimulation (aDBS) in patients with PD. The randomized study is being conducted at 12 study sites at movement disorders research centers in the US, Europe, and Canada, and plans to enroll 36 subjects for a 15-month evaluation. The primary end point will be the comparison of aDBS to standard continuous DBS for hours of ON time without troublesome dyskinesias, efficacy, and AEs by patient reports.2

For a full list of references, see the article on NeurologyLive.com.
NEW INDICATION

Dissolving the line between acute and preventive treatment for migraines

Finally, the first and only medication proven:

FAST
• One rapidly dissolving tablet that works quickly to resolve pain and return many patients back to normal activities in 1 hour
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See study results below.

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*Exploratory analysis. Subjects had ≥1 day of efficacy data in the observation period and in the first week of the double-blind treatment period.

Up to 18 doses of Nurtec ODT can be taken per month.

For the acute indication, Nurtec ODT was evaluated in a multi-center, double-blind, randomized, placebo-controlled study of 1351 patients (Nurtec ODT 75 mg, n=669; placebo, n=682), with co-primary endpoints at 2 h for Nurtec ODT vs placebo: pain freedom (21% vs 11%, P<.001) and freedom from most bothersome symptom (MBS; predefined as photophobia, phonophobia, or nausea; 35% vs 27%, P=.001). For the preventive indication, Nurtec 75 mg was evaluated in a multi-center, double-blind, randomized, placebo-controlled study of 695 patients (Nurtec 75 mg, n=348; placebo, n=347) with the primary endpoint being change from baseline in the mean number of monthly migraine days during weeks 9-12 (-4.3 vs -3.5, P=.01).

So you can TREAT PREVENT

Visit Nurtec-HCP.com to learn about the range of resources available to you, your office staff and your patients.
If you have questions or would like to connect with a representative, contact us by calling 1-833-4NURTEC or by emailing us at hcpsupport@biohavenpharma.com

INDICATION
Nurtec ODT is indicated in adults for the:
• acute treatment of migraine with or without aura
• preventive treatment of episodic 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.
Real patients like Ellie are managing their migraines with Nurtec ODT

Ellie is an actual patient who takes Nurtec ODT for either acute or preventive treatment of her migraines.

“Nurtec ODT meets my personal needs. I know that stress is a trigger during the school year—especially before college exams. I want to control my migraine on MY TERMS.”

- Ellie W

INDICATION
Nurtec ODT is indicated in adults for the:
• acute treatment of migraine with or without aura
• preventive treatment of episodic migraine

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 reactions were nausea (2.7% in patients who received Nurtec ODT compared to 0.8% in patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received Nurtec ODT compared to 0.8% 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 next page.


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

1.2 Preventive Treatment of Migraine
NURTEC ODT is indicated for the preventive treatment of episodic migraine in adults.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing for Acute Treatment of Migraine
The recommended dose of NURTEC ODT is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The safety of using more than 18 doses in a 30-day period has not been established.

2.2 Recommended Dosing for Preventive Treatment of Episodic Migraine
The recommended dosage of NURTEC ODT is 75 mg taken orally every other day.

4 CONTRAINDICATIONS
NURTEC ODT is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or any of its components. Delayed serious 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.

Acute Treatment of Migraine
The safety of NURTEC ODT for the acute treatment of migraine in adults 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 [see Clinical Studies (14)]. 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 (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 1,131 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)].

Preventive Treatment of Episodic Migraine
The safety of NURTEC ODT for the preventive treatment of episodic migraine in adults has been established in a randomized, double-blind, placebo-controlled trial with an open-label extension (Study 2) using a different oral dosage form of rimegepant [see Clinical Studies (14)]. In the 12-week, double-blind treatment period, 370 patients with migraine received one 75 mg dose of rimegepant every other day. Approximately 81% were female, 80% were White, 17% were Black, and 28% were Hispanic or Latino. The mean age at study entry was 41 years (range 18-74 years of age). Long-term safety was assessed in an open-label extension study that included 603 patients who were treated for up to one year. Overall, 527 patients were exposed to rimegepant 75 mg for at least 6 months, and 311 were exposed for at least one year.

The most common adverse reactions (occurring in at least 2% of rimegepant-treated patients and at a frequency of at least 1% higher than placebo) in Study 2 were nausea (2.7% in patients who received rimegepant compared with 0.8% of patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received rimegepant compared with 0.8% of patients who received placebo).

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 [see Clinical Pharmacology (12.3)].

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 [see Clinical Pharmacology (12.3)].

7.2 CYP3A 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 [see Clinical Pharmacology (12.3)].

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 [see Clinical Pharmacology (12.3)]. Avoid NURTEC ODT with inhibitors of P-gp or BCRP.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women. There is limited experience with 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 [see Clinical Pharmacology (12.3)].

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) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE
There is limited clinical experience with NURTEC ODT overdose. 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 [see Clinical Pharmacology (12.3)].

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The Glymphatic System and Sleep Cycle’s Role in Dementia Risk

By Matt Hoffman

AT THE 3RD Annual International Congress on the Future of Neurology®, experts in the care of sleep medicine offered insight into sleep and the glymphatic system’s roles in the development of dementias.

The importance of sleep for those at risk of developing Alzheimer disease and dementia cannot be understated. The opening session at the 3rd Annual International Congress on the Future of Neurology®, held September 17-18, 2021, offered an in-depth look at the current knowledge of the role of sleep as an essential part of the biologic function of human beings and all mammals. Without it, there are myriad systemic consequences, and although these points are well known, the underlying mechanisms of sleep and the biologic drivers of its operation are less understood.

A focus of this Medical Crossfire® session was on the recently discovered glymphatic system—a macroscopic waste clearance system that utilizes astroglial cell-mediated perivascular tunnels to stimulate the efficient elimination of soluble proteins and metabolites from the central nervous system. Besides these duties, the glymphatic system appears to enable brain-wide distribution of several compounds, such as glucose, lipids, amino acids, growth factors, and neuromodulators.1-3 Notably, though, the system functions mainly during sleep, aiding the ongoing elimination of neurotoxic wastes, such as amyloid-β, insinuating a potential connection to neurodegenerative conditions following the interruption of such processes driven by a lack of sleep.

“One of the exciting data points that gave us a sense as to what might be the mechanism was the discovery that amyloid-β clearance from the brain is preferentially higher during sleep. These poisons that accumulate during wakefulness are preferentially excreted from the brain during sleep in animals,” Karl Doghramji, MD, medical director at the Jefferson Sleep Disorders Center, and professor of psychiatry and human behavior and associate professor of neurology at Thomas Jefferson University, said in the session. “For many years, we’ve known that the brain has to get rid of these toxic compounds, and we know there are certain mechanisms, like local proteolytic degradation and phagocytosis, but those did not account for the majority of poisons that build up in the brain.”

Doghramji noted that the potential ramifications of disruptions to the sleep process are numerous, including the possibility that poor sleep may mediate the buildup of amyloid-β and tau plaques in the brain, thus driving the development of diseases, such as Alzheimer. He also pointed out that getting proper sleep can be a common challenge for individuals as they age, presenting a potential additional mechanism of disease progression.

Carlos H. Schenck, MD, senior staff psychiatrist at Hennepin Healthcare and Minnesota Regional Sleep Disorders Center, and professor of psychiatry at the University of Minnesota, noted that recent research has identified an association with average sleep duration in middle and older age with the incidence of dementia, ultimately finding there was a higher risk of dementia associated with sleep of less than 6 hours at ages 50 and 60 years compared with sleep of 7 hours or more.4 Additional data have implied that the alteration of peripheral metabolic signals induced by sleep restriction are responsible for cognitive deficit and Alzheimer disease development.5

“We need to send a message to all physicians—particularly primary care physicians—to assess the sleep duration by and large for most nights for their patients and emphasize that they need to get as much as 7 hours of sleep or more to help them later on in life,” Schenck said.

For more from the 2021 Congress, visit neurologylive.com/ifn

For a full list of references, see the article on NeurologyLive.com.
Optimizing the Migraine Consultation

Proper diagnosis and effective treatment planning can drastically improve quality of life for individuals with migraine.

By Marshall C. Freeman, MD, FAHS, FAAN, FAANEM
Director, Headache Wellness Center, Greensboro, NC

According to the World Health Organization Global Burden of Disease Study (2019), migraine is the second-highest cause worldwide for years lived with disability (YLD) among all ages, as well as the greatest cause of YLD for individuals aged 15 to 49 years.¹ ² Up to 1 billion individuals worldwide experience migraine,³ and direct and indirect costs of migraine are estimated to range from $28 billion to $36 billion annually in the United States alone.³ ⁴ Statistical regression modeling has estimated missed workdays due to migraine (absenteeism) at 1 to 2 days and lost productivity (presenteeism) at 2 to 5 days monthly depending on episodic or chronic migraine status,⁴ with high-end estimates predicting nearly $6500 of lost productivity yearly per individual affected with chronic migraine.⁵

Diagnosing and treating migraine correctly yields substantial benefits to the individual, family, and community. This review will provide an abbreviated approach to the migraine patient consultation, highlighting key clinical strategies that can enhance the management of patients with migraine.

Making the Diagnosis

Determine whether the patient has a primary or secondary headache. Practitioners can screen for secondary headaches using the acronym SNOOP.⁶ In its simplest form, SNOOP provides a broad differential diagnosis for secondary headaches: systemic symptoms/secondary risk factors, neurological signs or symptoms, onset (temporal qualities), older age of onset, and prior headache history. Red flags of the medical history include malignancy, immunosuppression, HIV/AIDS, pregnancy, fever, or weight loss; sudden, rapidly escalating or exploding head pain occurring spontaneously or with exertion (including thunderclap headache); later age of onset (> 50 years) for those without a prior history of headaches; and unusual or atypical head pain for individuals with known prior headaches. Red flags of the physical examination include impaired mental status, abnormal cranial nerve findings (including pupillary, eye movement, or visual field abnormalities), papilledema, temporal artery tenderness, and focal weakness.

Conditions that cause secondary headaches include tumors (including those of the posterior fossa), metastatic disease, brain abscess, encephalitis, subarachnoid hemorrhage, venous sinus thrombosis, idiopathic intracranial hypertension, low cerebrospinal fluid pressure headache, reversible cerebrovascular syndrome, stroke, and temporal arteritis. While complex neurological disorders with associated headaches do exist, distinguishing migraine from the above disorders can be achieved by careful attention to the differences in onset and exam findings.

Imaging is not indicated for migraine. The American Headache Society (AHS) has published guidelines for imaging in migraine.⁷ Many patients with migraine present with a typical medical history that can fulfill International Classification of Headache Disorders, third edition (ICHD-3) diagnostic criteria for diagnosis of migraine and normal results of physical examination. Routine use of imaging leads to unnecessary use of medical resources and higher societal medical costs. Incidental findings may lead to unhelpful and expensive further work-up and an increase in patient anxiety.⁷ For patients with headache with atypical features, MRI is the recommended imaging study over CT.⁷

Migraine is a diagnosis which requires taking a good history of the disease. There are currently no diagnostic laboratory tests or
imaging studies in clinical practice that establish the diagnosis of migraine. The ICHD-3 provides guidance on the diagnosis of all migraine types, including migraine without aura, migraine with aura, chronic migraine, and multiple migraine subtypes that are beyond the scope of this article.⁶

ICHD-3 defines migraine without aura as a recurrent headache disorder with attacks lasting from 4 to 72 hours untreated. Two of the following 4 elements should be present: (1) unilateral location, (2) pulsating quality, (3) moderate or severe pain intensity, and (4) aggravation by or causing avoidance of routine physical activity. Additionally, 1 of the following 2 elements should be present: (1) nausea and/or vomiting, and (2) photophobia and phonophobia. These guidelines allow for a broad inclusion of individuals experiencing headache to be given a diagnosis of migraine. Importantly, no single element is required for a diagnosis of migraine. An individual with migraine may lack nausea or vomiting or throbbing pain or unilateral location and still fulfill the ICHD-3 definition for migraine. A patient with bilateral nonpulsatile headache may have migraine if the other elements are present. Many patients receive misdiagnoses of other headache types because clinicians are unaware of the ICHD-3 criteria or are using the criteria incorrectly.

Treatment Decisions
The general neurologist or provider should treat migraine principally using evidence-based on-label therapies. As there are now numerous FDA-approved products for both acute and preventive treatments, practitioners can now use targeted therapy. Off-label medication use should be limited. While the provider should be sensitive to patient comorbidities, do not substitute inferior medications for the sole purpose of treating multiple ailments.

A headache calendar is an essential tool and the gold standard to determine whether a patient has episodic migraine (≤ 14 headaches per month) or chronic migraine (≥ 15 headaches per month). Headache calendars provide an accurate measure of headache frequency and allow providers to determine whether other meaningful patterns exist, such as weekend-related headaches or those related to menstruation. Patients can track headache activity with paper or phone-based applications. During the initial interview, the provider should ask the patient to estimate the number of pain-free days experienced each week, as many patients routinely underestimate the number of headache days they experience. It is the author’s observation that many patients commonly underreport headache frequency because many events have become chronic or mild in intensity, lack the most burdensome migraine qualities, or have been suppressed by over-the-counter (OTC) medications.

Preventive Treatments
Preventive treatment management should take priority over abortive treatment management. Effective prevention reduces migraine frequency, migraine severity, and migraine duration; reduces prolonged or disabling aura attacks; reduces likelihood of status migrainosus; and may improve effectiveness of acute treatments. Focusing on prevention also reduces the risks of acute treatment pitfalls, especially medication-overuse headache (MOH) with prescription and OTC medications.

The AHS and the American Academy of Neurology have jointly published evidence-based guidelines for migraine prevention.⁹ Level A (established efficacy) medications include topiramate, divalproex sodium, sodium valproate, metoprolol, propranolol, and timolol; level B (probably effective) medications include amitriptyline, venlafaxine, atenolol, and nadolol. Newer FDA-approved products that would be included under level A efficacy include onabotulinumtoxinA (Botox; Allergan) for chronic migraine and the calcitonin gene-related peptide (CGRP) medications erenumab (Aimovig; Amgen/Novartis), fremanezumab (Ajovy; Teva Pharmaceuticals), galcanezumab (Emgality; Eli Lilly and Company), and eptinezumab (Ypepti; Lundbeck Seattle BioPharmaceuticals). Rimegepant (Nurtec ODT; Biohaven Pharmaceuticals), a small molecule CGRP ligand antagonist, is indicated for both the acute and preventive treatment of migraine. Select FDA-approved neuromodulating therapies for prevention include noninvasive vagus nerve stimulator (gammaCore Sapphire; electroCore, Inc), single-pulse transcranial magnetic stimulation (sTMS) mini, and transcutaneous supraorbital nerve stimulation (Cefaly Dual) devices.

Avoid polypharmacy and stacking preventive medications. Rather, use a single preventive medication to its maximum tolerable dose to determine its efficacy and then change to a different product if needed. Successful treatment outcomes for preventive medications in migraine are a 50% reduction in mean headache days.¹⁰ Begin medications at a low dose and titrate slowly to improve tolerability. Discontinue a medication that demonstrates only incomplete benefit in favor of a new medication trial. Returning to the original medication is always possible if the subsequent choice is less effective. Avoiding polypharmacy reduces potential adverse effects, improves adherence, and reduces cost. The strategy of combining medications solely because they may have different mechanisms of action is not supported at this time because the definitive mechanism of action for migraine is unknown for most commonly used preventive treatments (with the exception of the newest CGRP medications).

Providers should regularly evaluate treatment effectiveness for preventives. Many patients will return to the clinic stating their therapies are not working. Interview patients carefully to define the cause of a treatment failure, and avoid rushing to switch treatments. Failure may be related to zero efficacy, incomplete efficacy, inadequate dose, inadequate trial period, medication tolerability, presence of medication overuse, nonadherence, incomplete treatment of associated comorbid conditions, or unreasonable patient (or physician) expectations. Set reasonable expectations with patients at the onset of therapy to reduce patient and provider dissatisfaction. Most medication failures can be salvaged by identifying the issue and adjusting the approach.

Both patient and provider should be aware of medication trial periods needed for effectiveness. Oral products may require 2 to 3 months of use to determine efficacy, whereas newer CGRP medications may take 3 to 6 months. Personal experience suggests
Acute Treatment

Finding the most effective acute antimigraine treatment may take multiple attempts. Practitioners should individualize medications for the patient. A detailed history including the patterns of headache, time of onset, presence of nausea or vomiting, and occurrence of rapidly escalating pain should be elicited. Antimigraine agents are currently available in tablets, oral dissolving tablets, nasal sprays, nasal powders, and injectable formulations. Patients with significant nausea or vomiting should be prescribed nasal or injectable treatments to bypass impaired gastrointestinal absorption; likewise, patients with rapidly escalating migraine attacks should preferentially use nasal sprays or injections because of better early efficacy and faster onset compared with oral therapies.

Triptan medications remain the first-choice treatment for many patients with migraine (eg, sumatriptan, zolmitriptan, rizatriptan, etc). Triptans are effective, well tolerated, typically non-sedating, readily available, and low cost. Avoid prescribing different triptans to the same patient concomitantly (eg, sumatriptan plus rizatriptan) because of risks of triptan-to-triptan contraindications and medication overuse headache (MOH); however, it is ideal to prescribe different formulations of the same triptan (sumatriptan injection plus sumatriptan tablets), which the patient can then select preferentially for acute attacks. Both sumatriptan and zolmitriptan are available in multiple formulations.

A subset of patients with migraine may have triptan contraindications (including cardiovascular or cerebrovascular) or triptan intolerances. These patients may be candidates for the newer branded CGRP medications. Avoid opioids and butalbital-containing medications. Neuromodulation for acute treatment of migraine is currently underused. On-label acute options include the gammaCore, sTMS mini, Cefaly Dual, Nerivio, and Relivion devices. The role of neuromodulation for both acute and preventive treatment is still developing.

Medication overuse is a significant contributor to migraine disability. The ICHD-3 defines MOH as a primary headache that, in association with medication overuse, progresses to a new type of headache or a significant worsening of the preexisting headache. Patients with MOH experience greater migraine frequency and burden than those with controlled acute medication usage.

MOH (formerly known as rebound headache) can develop from regular intake of any combination of ergotamines, triptans, combination analgesics, or opioids over a total of 10 or more days per month for more than 3 months. MOH can develop from regular intake of acetaminophen, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and other analgesics over a total of 15 or more days per month for more than 3 months. Data from the American Migraine Prevalence and Prevention Study demonstrated that opioid use for as few as 8 days per month and butalbital-combination medication use for greater than 4 days per month were sufficient to cause MOH and progression to chronic migraine. Comprehensive studies are not currently available to determine the risk of MOH with newer CGRP products, such as rimegepant, ubrogepant (Ubrelvy; AbbVie), or other forthcoming medications.

Patients who switch among various oral products are not protected against MOH either. MOH can develop from overuse of combination categories. Avoid prescribing multiple triptans, multiple acute CGRP ligand antagonists, opioids, butalbital, or similar medications to an individual patient. Teach patients to be selective in managing attacks. Treating attacks early provides the best efficacy. Treating early also reduces the likelihood of requiring additional doses of medication or requiring rescue treatment. Not every headache requires oral medication. Patients with high-frequency attacks may use non-oral options, such as topical ointments or salves, massage, relaxation exercises, and possibly neuromodulation. Prioritize prevention over abortive treatment.

Comorbidities and Lifestyle Management

Proper migraine treatment requires acknowledgment and management of comorbid disorders and unhealthy lifestyle choices. Migraine is comorbid with dozens of psychiatric, neurologic, pain, and medical conditions, including depression, anxiety disorder, bipolar disorder, panic attacks, epilepsy, insomnia, sleep apnea, restless leg syndrome (RLS), fibromyalgia, obesity, stroke, and myocardial infarction. In many circumstances, the neurologist may be the first provider to formally identify sleep disorders. Testing for sleep apnea, RLS, and other sleep conditions should be pursued. Modifiable elements should be targeted, such as addressing shift-work hours, unregulated sleep times involving the weekends, and poor sleep environments populated by televisions and cell phones. When appropriate, the focus should be on introducing behavioral treatments before medications.

Obesity is an epidemic in the United States, with a prevalence of 42.4% in 2017-2018, with non-Hispanic Black adults having the highest age-adjusted prevalence of obesity at 49.6%. Obesity is a risk factor for migraine and is associated with an increase in migraine attack frequency and severity, as well as progression
from episodic migraine to chronic migraine. Honest discussions with patients with obesity who have migraine are beneficial. Removing processed and high-calorie foods reduces obesity risk. Referral to a nutritionist may be helpful.

Other areas of lifestyle modification appropriate for discussion include tobacco use, smoking, vaping, sedentary behavior, stress management, caffeine use, soda and other beverage consumption, and chronically poor nutritional choices.

In summary, a treatment approach that diagnoses correctly, uses evidence-based therapies, limits polypharmacy, and actively identifies and manages comorbid conditions will increase the likelihood of successful outcomes for patients with migraine.

REFERENCES

For more direct access to expert insight into headache, go to the NeurologyLive® “Headache/Migraine” Clinical Focus page.
Explore MS Website

Managing the neuroinflammation of today may help slow the irreversible neurodegeneration of tomorrow.

Visit the MS website to explore early MS neuropathology, disease progression, and patient perspectives through interactive tools that span the spectrum of MS.

Truths vs Myths

Truths and Myths of MS
Challenge your understanding of MS in this game that includes questions on the diagnosis, management, and some needs of patients with MS.

Disease Progression in MS
Explore this case example of RRMS illustrating how early neuroinflammation may progress to irreversible neurodegeneration and clinical disease progression over time.

Immunoglobulins in MS
View this PDF to learn about the role of immunoglobulins in patients with MS.

Mechanism of Disease in MS
Explore how autoreactive immune cells trigger early neuroinflammation in MS.

MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.
S1P Receptor Modulation in Multiple Sclerosis

By Jennifer S. Sun, PhD

MULTIPLE SCLEROSIS (MS) IS THE MOST COMMON autoimmune-mediated disorder of the central nervous system (CNS), affecting approximately 2.3 million people worldwide with nontraumatic disabling neurological impairment.1,4 Although the precise cause of MS remains unclear, most patients are believed to have inherited a genetic predisposition for the disorder.1,2 The neurological symptoms of MS are thought to be triggered by an autoimmune response in the white matter of the brain and spinal cord that causes axonal demyelination, degeneration, and incomplete paralysis.1,2,4 Briefly, the body’s immune system attacks myelin, the protective sheath surrounding nerve fibers, to potentially permanently short-circuit the nervous system.2,4 Presently, MS has no known cure.1,2 Drugs have been developed to manage the major symptoms of MS, although not completely satisfactorily: some therapies are not well tolerated, others are initially effective but become less so as the disease progresses, and yet other maladies are difficult to treat until the underlying cause is elucidated.2,5,10 Now, a focus on disease-modifying therapy seeks to do more than just manage symptoms, instead attempting to alter either the frequency of relapses or the rate of progression.2,3 Yet, drug development for MS is particularly challenging because the known causal gene targets are regulatory molecules in multiple biological pathways, so there is a heightened risk of off-target physiological effects.3,6,8

The clinical course of MS is highly heterogeneous but can be broadly classified into relapsing and progressive forms.2,3 In relapsing-remitting MS (RRMS), episodes of neurological disability are separated by periods of clinical stability.2,6 RRMS eventually transitions into secondary progressive MS (SPMS) as disability progressively worsens.2,6 Early treatment of patients with RRMS can potentially prevent, reduce, or delay progression to SPMS.2 However, the axonal loss and demyelination resulting from chronic inflammation in SPMS may be irreversible.2,6

Sphingosine 1-phosphate (S1P) is a bioactive lysophospholipid signaling molecule that is critically involved in a wide range of physiological and pathophysiological events (FIGURE).8 Erythrocytes and endothelial cells are the major sources of S1P in the plasma,5,8 whereas mast cells and platelets contribute to elevated local production of S1P under inflammatory conditions.3 Phosphorylation of sphingosine by kinases produces this potent signaling molecule, which acts as an extracellular first messenger and intracellular second messenger.5 S1P functions as a ligand for a group of cell surface heterotrimeric G protein-coupled receptors called S1P receptors (S1PRs), which propagate the ligand-binding signal.3,5 In so doing, S1P regulates hormone synthesis and activation,5,10 embryonic development of the cardiovascular system and the central nervous system (CNS), vascular permeability, vascular smooth muscle tone, and immune cell trafficking.5 Elevated S1P levels in cerebrospinal fluid and brain parenchyma of patients have been associated with MS progression.8,10

FIGURE. Sphingosine 1-phosphate (S1P) Binding to S1P receptor (S1PR) Subtypes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor</th>
<th>Location</th>
<th>Signaling pathway</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimoda</td>
<td>S1P1</td>
<td>T cells, B cells, natural killer cells, macrophages/monocytes, dendritic cells, endothelial cells, astrocytes, microglia, smooth muscle cells, neurons, astrocytes, microglia, oligodendrocytes</td>
<td>G12/13</td>
<td></td>
</tr>
<tr>
<td>Fingolimoda</td>
<td>S1P2</td>
<td>B cells, macrophages/monocytes, dendritic cells, endothelial cells,smooth muscle cells, neurons, astrocytes, microglia</td>
<td>G12/13</td>
<td></td>
</tr>
<tr>
<td>Fingolimoda</td>
<td>S1P3</td>
<td>B cells, macrophages/monocytes, dendritic cells, endothelial cells,smooth muscle cells, neurons, astrocytes, microglia, oligodendrocytes</td>
<td>G12/13</td>
<td></td>
</tr>
<tr>
<td>Fingolimoda</td>
<td>S1P4</td>
<td>T cells, B cells, natural killer cells, macrophages/monocytes, dendritic cells, endothelial cells,astrocytes, microglia, smooth muscle cells, neurons, astrocytes, microglia, oligodendrocytes</td>
<td>G12/13</td>
<td></td>
</tr>
</tbody>
</table>

S1P binds different S1PR subtypes, with distinct regulatory effects on immune response, vascular tone, and cell migration. Small-molecule modulators bind specific S1PR subtypes to alter S1P signaling. As a result, inflammatory cell migration into the central nervous system is mitigated, thus providing a direct benefit to patients with multiple sclerosis (MS).

4 Requires phosphorylation in situ for activity.

Five S1PR subtypes exist, S1PR1 to 5, which vary in terms of expression pattern and functional role. S1PR modulators display varied effects depending on the subset of S1PR subtypes they target. S1PR1 is expressed in the endothelium, where it recruits dendritic cells and controls vascular permeability and heart rate, and it is also found on lymphocytes, where it mediates migration from lymph nodes. S1PR2 is expressed in the CNS and plays essential roles in the mediation of neuronal excitability, but it has no known role in immune function. S1PR3 is found on cardiac myocytes and endothelial and vascular smooth muscle cells, where it regulates myeloid differentiation, although most of its activities parallel those of S1PR1. S1PR4 is expressed on immune cells in lymphoid tissues, where it functions in regulating cytokine expression. Finally, S1PR5 is expressed on oligodendrocytes in the CNS; it regulates the function and migration of these cells. There is some redundancy among the signaling pathways associated with different S1PR subtypes. Moreover, S1PR1, S1PR3, and S1PR5 subtypes share structural similarity. For these reasons, the design of highly specific therapeutics targeting each S1PR subtype is difficult. Most S1PR modulators in clinical development or approved for MS treatment primarily target S1PR1, with concurrent effects on 1 or more other S1PR subtypes, particularly S1PR3.

S1PR modulation therapies have been approved for MS. Small-molecule therapeutics bind to and alter signaling through specific S1PR subtypes. The goal of this therapeutic approach is to inhibit immune cell trafficking and improve neuroprotection. Indeed, S1PR modulators have been demonstrated to enhance neuronal survival and mitigate gliosis and demyelination in a mouse model of MS. A separate study in patients with nonrelapsing forms of SPMS captured a direct benefit of S1PR modulators—reduction of neuronal damage when compared with placebo. The most prominent therapeutic target is S1PR1. Small-molecule modulators functionally antagonize S1PR1 signaling by binding to this receptor on lymphocytes, which then causes receptor internalization and prevents lymphocyte egress from lymph nodes. The resulting sequestration of autoreactive lymphocytes limits inflammatory cell infiltration into the CNS.

One caveat of this is approach is that these agents often affect S1P signaling in a variety of nontarget tissues due to the diverse expression pattern of S1PR1 and thus can trigger adverse effects (AEs). For example, S1PR modulators can cause slowed heart rate upon initiation of therapy due to S1PR1 expression on atrial myocytes. S1PR modulators can also cause progressive multifocal leukoencephalopathy due to John Cunningham virus reactivation, as well as macular edema and increased blood pressure. Second-generation agents can potentially improve the convenience, safety, and tolerability of MS therapeutics.

Fingolimod (FTY720; Gilenya) is the first-in-class S1PR modulator for treatment of RRMS. A structural analogue of endogenous sphingosine, fingolimod is a lipophilic molecule that can readily cross the blood-brain barrier, where it is phosphorylated by sphingosine kinases into its active form, fingolimod-P. Fingolimod exhibits high oral bioavailability (93%), with a time to maximum plasma concentration (Tmax) of 12 to 16 hours, and reaches steady state after 1 to 2 months of regular dosing. However, active fingolimod-P is found at relatively low concentrations. Recovery of mean lymphocyte count after treatment discontinuation can take 4 to 8 weeks. Severe rebound effects can occur up to 12 weeks after discontinuation, perhaps due to changes in peripheral lymphocyte phenotypes that promote disease activity. A series of large, multicenter, randomized, double-blind phase 3 clinical trials examined the safety and efficacy of fingolimod for: the treatment of PPMS (INFORMS [NCT00731692]), RRMS (FREEDOMS [NCT00289978], FREEDOMS II [NCT00355134], TRANSFORMS [NCT00340834]), including for RRMS in pediatric populations (PARADIGMS [NCT01892722]). FREEDOMS and FREEDOMS II revealed a significant reduction in annualized relapse rate (ARR) of RRMS at 24 months and improvements in inflammatory disease activity and tissue damage. The frequency of new or enlarged T2 lesions and Gad-enhancing (GdE) lesions were both significantly reduced. Fingolimod exhibited sustained efficacy in the long term (10 years) with no new safety concerns. In patients younger than 30 years, a greater long-term benefit is expected with early initiation of fingolimod therapy. However, both adult and pediatric
Treating SPMS: Novel Approaches to Improve Disease Management

Second-generation S1PR modulators have been developed to improve on S1PR subtype specificity and increase bioavailability while minimizing AEs.9 Ceralifimod and amiselimod are 2 such immune cell–trafficking modulators with selectivity for S1PR1 and S1PR5.3 Both demonstrated risk profiles similar or superior to those of other S1PR modulators in phase 2 trials, yet clinical testing was discontinued for strategic reasons.5 The phase 2 DreaMS17 trial (NCT01081782) enrolled 407 patients aged 18 to 55 years, with active RRMS and an Expanded Disability Status Scale (EDSS) score below 6, to evaluate the efficacy and safety of ceralifimod (ONO-4641, Merck) over 26 weeks.5,17 A total of 360 patients completed the study, experiencing significant reductions in total number of GdE lesions at doses of 0.05 mg and 0.15 mg.5 The efficacy of ceralifimod was sustained for 26 weeks.5 The risk profile was similar to other S1PR modulators.3 The phase 2 MOMENTUM18 trial (NCT01742052) enrolled 415 patients aged 18 to 60 years with active RRMS and an EDSS score below 6, to assess the safety and efficacy of amiselimod (MT-1303, Biogen) over 24 weeks, followed by a 72-week dose-blinded extension.8 Similar to fingolimod, amiselimod requires phosphorylation to form its active metabolite, amiselimod-P.3 A total of 367 patients completed the study, experiencing significant reductions in GdE lesions (61% for 0.2 mg, 77% for 0.4 mg) and ARR (67% for 0.2 mg, 56% for 0.4 mg).5,18,19 Remarkably, despite the prevalence of respiratory infection with fingolimod, no serious AEs, including infections, were reported with amiselimod.3

Ponesimod (Ponvory, ACT-128800, Actelion) is another orally active S1PR modulator with high affinity for S1PR1.5,6,8 Ponesimod is rapidly absorbed and reaches maximal availability within 2.5 to 4 hours.5 Due to its short half-life of 32 hours, lymphocyte count restabilizes at baseline within 1 week of discontinuation.5 Maximum reduction (70%) in total lymphocyte count occurs by day 8 (range, 7-14 days) after the first dose.5 Two large, multicenter, randomized, double-blind, parallel-group, active-controlled, superiority, phase 3 studies (OPTIMUM and POINT) evaluated the safety and efficacy of ponesimod in treating RRMS.5 At total of 1133 patients were recruited for the OPTIMUM trial [NCT02425644]20 to receive once-daily ponesimod 20 mg for 108 weeks compared with teriflunomide.5 Patients experienced significant reduction in ARR (30.5%), fatigue-related symptoms, and combined unique active lesions (56%).5 The add-on POINT study [NCT02907177]21 then aimed to distinguish the benefit of ponesimod in combination with dimethyl fumarate (Tecfidera) for at least 6 months, but the study was terminated because of low recruitment rates.5 Overall, ponesimod exhibited a favorable safety profile at doses of 10 mg and 20 mg.5 First-dose bradycardia and atrioventricular block are common AEs, although optimized titration could mitigate the first-dose effect on heart rate.5

Siponimod (BAF312, Mayzent), a de novo derivative of fingolimod, is the first oral treatment specifically approved for treatment of SPMS.8 Siponimod is an immune cell–trafficking, highly bioavailable, high-affinity, selective S1PR1 and S1PR5 agonist that does not require phosphorylation for activation.5 Maximum availability is achieved in 3 to 8 hours.5 An up titration of siponimod is required to mitigate its cardiac effects;5,6 steady-state plasma concentration is reached after a 10-day titration regimen.5 Siponimod has a short half-life of 22 to 38 hours, so lymphocyte count restabilizes after 3 to 4 weeks.5 Siponimod reduces peripheral lymphocyte count to 70%, which, in turn prevents neurodegeneration.5 By binding S1PR5 on oligodendrocyte precursor cells, siponimod also promotes remyelination.5 The 60-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 EXPAND study [NCT01665144]22 recruited 1653 patients aged 18 to 60 years with SPMS and an EDSS score of 3.0 to 6.5.5 Sixty-four percent of subjects had not relapsed in 2 years prior to enrollment.5 Siponimod delayed disability progression by 21% in time to 3-month confirmed disability progression (CDP) and 26% in time to 6-month CDP; reduced GdE (89%) and T2 (57%) lesions; and reduced ARR (55%).5 The risk profile of siponimod is consistent with other S1PR modulators.3 However, an assessment of cardiac function and varicella-zoster virus antibody status is recommended prior to treatment initiation.5,6

Ozanimod (RPC1063, Celgene), another orally active, highly bioavailable, small-molecule S1PR1 and S1PR5 modulator that does not require phosphorylation for activation, is approved for use in adults with RRMS, clinically isolated syndrome, and SPMS.5,6 Ozanimod reaches Tmax at 6 to 8 hours.5 Despite its higher volume of distribution, ozanimod absorption is slow, which could account for its increased tolerability in terms of reduced first-dose effects on heart rate.5 Other advantages include its short half-life of 19 to 22 hours, requiring only 2 to 3 days for lymphocyte recovery after discontinuation.5 The multicenter, randomized, double-blind, double-dummy, parallel-group, active comparator phase 3 SUNBEAM study (NCT02294058)23 enrolled 1346 patients with RRMS to evaluate the efficacy and safety of ozanimod over 26 weeks.5 Both doses significantly reduced new or enlarging T2 lesions (25%-48%) and GdE lesions (34%-63%) and reduced ARR (0.17 at 1 mg; 0.22 at 0.5 mg).5 Ozanimod has an overall favorable safety profile, with no reports of serious opportunistic infections, macular edema, abnormalities in pulmonary function tests, or malignancy.5 Overall, S1PR modulators are unique disease-modifying therapies that present effective, convenient, generally tolerable means to mitigate MS.5,6 Continued improvement in the pharmacodynamics and pharmacokinetics of S1PR modulators, particularly in modulator-receptor selectivity, should improve therapeutic efficacy while reducing the potential for AEs.8 ■

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For a full list of references, see the article on NeurologyLive.com.
Breaking gene therapy news and expert-driven insights at your fingertips

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SPINRAZA—Strong history, powerful evidence

SPINRAZA has been studied in infants and children in the longest clinical trial program in SMA to date.\(^1\)\(^7\) SPINRAZA also has the most published real-world evidence in adults up to age 72 with SMA.\(^8\)\(^-\)\(^10\) Explore the history below.

<table>
<thead>
<tr>
<th>OCT 2012</th>
<th>AUG 2014</th>
<th>NOV 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS2/CS12 SUPPORTIVE TRIALS ¹,²,¹¹</td>
<td>ENDEAR PIVOTAL TRIAL ³,⁴</td>
<td>CHERISH PIVOTAL TRIAL ⁴,⁵</td>
</tr>
<tr>
<td>28 patients 2 to 16 years</td>
<td>121 patients ≤7 months at first dose</td>
<td>126 patients 2 to 9 years at screening</td>
</tr>
</tbody>
</table>

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

SPINRAZA pivotal trials did not include adults with SMA.

**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%).

**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.
IMPORTANT SAFETY INFORMATION (cont’d)

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 the brief summary of Prescribing Information on the following pages.


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225 Binney Street, Cambridge, MA 02142
Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed. Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

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-control 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.

In clinical studies, 346 patients (47% male, 76% Caucasian) were treated with SPINRAZA, including 314 exposed for at least 6 months, 258 exposed for at least 1 year, and 138 exposed for at least 2 years. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days 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=64 for SPINRAZA, n=42 for control); an open-label study in presymptomatic infants (Study 3, n=25) and other studies in symptomatic infants (n=54) and later-onset patients (n=103). 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 at baseline 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 (Study 1)

<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, para influenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenza, pneumonia moraxella, pneumonia para influenzae 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 mg(^1) N=84 %</th>
<th>Sham-Procedure Control N=42 %</th>
</tr>
</thead>
<tbody>
<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 294 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Seventeen patients (6%) developed treatment-emergent ADAs, of which 5 were transient, 12 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.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.
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. Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. 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)].
The Comprehensive Management of Dravet Syndrome

In a NeurologyLive® Insights series, experts in the diagnosis and treatment of Dravet syndrome discussed the management of the disease and the utilization of approved treatments to improve outcomes in patients.

**DRAVET SYNDROME (DS),** also known as severe myoclonic epilepsy of infancy, is a rare form of intractable epilepsy that begins in infancy and proceeds with accumulating morbidity that significantly affects individuals throughout life. Approximately 80% of those who receive a diagnosis of DS have an SCN1A mutation, but the presence of a mutation alone is not sufficient for diagnosis, nor does the absence of a mutation exclude one.

Rare, atypical presentation of DS may be associated with other genetic mutations, such as SCN1B, GABRG2, and HCN1. Additionally, seizures lasting more than 10 minutes, those occurring on 1 side of the body, and those triggered by a warm bath in children under 12 months are clues to a DS diagnosis. Although the clinical presentation may be similar, some patients with atypical DS may require alternate paths of treatment.

Early diagnosis of DS is critical to proper treatment and achieving the best outcome. Although patients may be able to reduce seizure severity and number with appropriate therapy, they do not typically reach complete seizure freedom. To understand more about the management of the disease, a recent NeurologyLive® Insights series brought together Joseph E. Sullivan, MD, director of the Pediatric Epilepsy Center, University of California, San Francisco, and Elaine C. Wirrell, MD, director of pediatric epilepsy and professor of neurology, Mayo Clinic. The duo provided perspective on several topics that are vital to the care of patients with the disease.

**Early Presentation and Diagnosis of DS**
The classic presentation of DS is in an otherwise previously healthy, developmentally normal child. Affected children present first with an often prolonged and often hemiconvulsive seizure, which is frequently associated with fever, often low grade. After age 1, they typically develop other seizures such as myoclonic, absence, and focal-impaired awareness.

"At that point, we start to see the child whose development was normal but then starts to fall off. They’re not gaining those milestones as quickly as we had hoped,” Wirrell said. “That’s the characteristic presenting symptom, and there’s really no other underlying cause that people can find unless you do the genetic testing. The
MRIs are normal. Often times the EEGs [electroencephalograms], if you do them remote from seizures, are also normal.”

Febrile seizures are common for these patients and may be red flags for those who have not received a diagnosis. Although DS is a rare disease, it is more common than people may think. Sullivan was part of a study evaluating electronic medical systems and found a new diagnosis for every 15,700 people. Pediatric neurologists will likely encounter this type of patient in practice, Wirrell noted.

Genetic testing has become a crucial component in improving the diagnostic accuracy of DS and other types of epilepsy. Over time, testing has become more accessible and cost-efficient. Multiplex ligation-dependent probe amplification is an assay that determines the copy number of a particular gene and whether that gene has been deleted or duplicated.

Wirrell says that genetic testing should be done as early as possible, especially “in a very young child who has a prolonged febrile seizure, and particularly if it’s a prolonged hemiconvulsive febrile seizure.”

“Those are kids [in whom] I would even think about doing [genetic testing] from the get-go with their first seizure—certainly if there are recurrent prolonged febrile seizures or recurrent hemiconvulsive febrile seizures and particularly if they’ve switched sides,” Wirrell said.

The risk of sudden unexpected death in epilepsy (SUDEP) is higher in those who have DS compared with other epilepsies. Because of this, patients and caregivers alike must create an aggressive rescue plan with their epilepsy specialist to address key signs and symptoms to mitigate the risk of SUDEP. Diazepam (Valtoco; Neurelis) and other benzodiazepines are the go-to rescue medications.

“I know that in my practice, all my patients with Dravet have a seizure rescue plan that’s a little more detailed than maybe [that of] a patient with epilepsy. It even comes as a care coordination note in the electronic medical record that if they hit our [emergency department (ED)], this is what works for them,” Sullivan said.

“It’s important to have this individualized approach because we learn, unfortunately, that some of these patients come in within a prolonged seizure. You go through the normal algorithm that [ED] physicians are taught, and it doesn’t work for that patient, but something else does. I certainly think it’s important having that individualized treatment plan.”

Management and Goals of Treatment
In the past few years, 3 new medications have received FDA approval for the treatment of DS, with higher efficacy than that of previous first-line medications used. The first was cannabidiol (CBD; Epidiolex). In June 2018, the FDA greenlit the oral solution for the treatment of seizures associated with DS and Lennox-Gastaut syndrome. It marked the first FDA-approved agent containing a purified drug substance derived from cannabis.

“The goal is really to try to reduce that seizure burden, particularly the prolonged seizures, the ones that are taking the kids into the [ED], into the ICUs [intensive care units]; we want to get rid of those. The convulsive seizures as well,” Sullivan said. “We really want to reduce the seizure frequency because those are the ones that place those patients at highest risk of [SUDEP].”

CBD’s effectiveness was studied in 3 randomized, double-blind, placebo-controlled clinical trials involving 516 patients with Lennox-Gastaut syndrome or DS. CBD, taken along with other medications, was shown to be effective in reducing the frequency of seizures compared with placebo.

Wirrell noted that “it probably does have many mechanisms that we just don’t understand, but as long as we understand the safety profile, I’m OK with that. I’m OK with saying, ‘I don’t know why it works, but it works, and it seems to be safe, so let’s go with it.’”

The most recent drug to enter the market, Zogenix’s fenfluramine (Fintepla), received the go-ahead in June 2020 as an oral solution for patients 2 years and older. The medication was approved with a boxed warning for risk of valvular disease and pulmonary arterial hypertension and is distributed through the Fintepla Risk Evaluation and Mitigation Strategy program.

The robust data from fenfluramine’s clinical program satisfied both Wirrell and Sullivan. They noted the impact fenfluramine had on a proportion of patients who achieved at least 75% seizure reduction. To date, most studies evaluating investigational DS agents had looked at 50% responder rates, whereas fenfluramine demonstrated an extra bit of efficacy.

“I think so much about quality of life and Dravet is related to seizures and breakthrough seizures and prolonged seizures. I think that’s a very negative impact on quality of life for both the kids and the families,” Wirrell said. “I saw these kids actually being able to be kids and being able to get to school more often and participate in family activities more often. Families were getting better sleep. They certainly appeared better rested. So I think [there was] certainly improvement and alertness in the kids with [fewer] seizures. I think we have seen that even more as we’ve been able to address those seizures.”

Building on the momentum of the recent approvals, a handful of other investigational treatments and approaches are in the pipeline. Gene therapy has become an increasingly hot topic throughout neurology and may present opportunities for patients with DS, according to Sullivan. Although encouraged, he noted that he did not anticipate this type of progress 5 years ago.

“It is exciting to think about not only FDA-approved medications to treat seizures but something that could get at the root cause. I think there’s a lot of interest, certainly from us as clinicians and our colleagues, but even more interest on the part of the patient community because this is what they’ve been asking for, for so long,” Sullivan concluded.
Improving Stroke Systems of Care: A Tandem Role for Neurology and Primary Care Physicians

Mitchell S. V. Elkind, MD, MS, MPhil, shared his perspective and offered insights into the recent updates from the American Heart Association/American Stroke Association on the landscape of stroke prevention and poststroke care.

IN JULY 2021, the American Heart Association (AHA)/American Stroke Association (ASA) released a scientific statement outlining goal-directed and patient-centered care for poststroke management in adults. Entitled “Primary Care of Adult Patients After Stroke,” the statement calls specific attention to the role of the primary care provider in the poststroke phase.

According to Mitchell S. V. Elkind, MD, MS, MPhil, immediate past president, AHA/ASA; professor of neurology and epidemiology, and chief, Division of Neurology Clinical Outcomes Research and Population Sciences, Columbia University, the guidance is a useful tool for the primary care community, as they are generally more involved with patient care than neurologists are following a stroke, playing a pivotal role in educating patients, as well as controlling risk factors and associated complications such as depression and other mental health issues.

To find out more about the role that primary care can play and the need for communication and interplay between them and neurologists, NeurologyLive® spoke with Elkind about the AHA/ASA’s position.

Q: What should the clinical community take away from the recent AHA/ASA statement?

This statement is really about the role of the primary care provider in the care of the patient with stroke after they recover from their initial stroke and return home. It’s about how primary care physicians can play an essential role in the treatment of patients with stroke going forward. There’s a tremendous amount that primary care physicians can do.

First, most patients with stroke are cared for by primary care physicians, not by neurologists, especially in the long term. Primary care doctors are going to have a very important role in helping patients understand their new disabilities, if that’s the case, and their new life after stroke. They’re going to have an important role to play in controlling peoples’ risk factors, managing their medications to prevent them from recurrences, and managing some of the complications that can occur after somebody has a stroke, [such as] depression or other mental health problems, cognitive issues, or symptoms like pain and discomfort.

This statement is about explaining to that community how they can best help their patients going forward. Primary care doctors are in a great position to help patients who’ve had a stroke because stroke goes along with a lot of other chronic medical problems that primary care doctors are probably the best equipped to deal with. Conditions like high blood pressure, diabetes, high cholesterol—these are all very common, of course, in patients with stroke. Those physicians are well equipped to help patients manage this. They also know these patients well. They know their family situation, social situation, and employment situation, so they’re able to help their patients navigate through those kinds of issues. This statement is really a tool to help the primary care community in their care of these patients.

Q: How can the cerebrovascular community help the primary care community have a bigger role and understand their part in the poststroke care process?

In neurology, we think sometimes about something we call...
neurophobia, which is this idea that people who aren’t neurologists are scared of the brain, that it’s somehow too complicated and they just don’t want to know anything about it. But a lot of what primary care doctors are doing is very fundamental to the care of patients with stroke already. There are a lot of basic care issues like management of blood pressure, management of diabetes, management of lipids, management of some cardiac conditions like atrial fibrillation, and recommending exercise and a healthy diet—these things are all essential to stroke prevention and, really, brain health overall. Primary care physicians are already in a good position to do this kind of thing.

The new stroke prevention guidelines that recently came out, and one of the new developments in those guidelines, is the idea that stroke systems of care are effective in not only managing acute stroke but also in long-term prevention. A big development over the past couple of decades has really been this idea that we need to get patients into the emergency [department] right away when they have a stroke to be able to give them clot-busting medications like tPA [tissue plasminogen activator] or thrombectomy, extracting a clot from the brain. Our stroke systems of care were focused on prehospital care, the emergency [department], and those kinds of acute interventions. But stroke systems of care are also important for the transition from the acute hospital to rehabilitation, back to the home, and then the long-term care of the patient.

There are ways in which the acute neurological care of the patient, and the neurology team, can help the secondary care provider and the primary care provider afterward. For example, things like checklists that people can use after they go back to their primary care provider can be useful to set up a plan to manage patients going forward, and then use that as a reference point to make sure that the care is consistent with that plan. With the evidence-based guidelines that exist, opportunities for the primary care physician to speak with the neurologist and the neurology team and make sure that transition is smooth exist, too, so that everybody knows what medications the patient is being discharged on. In some cases, the medications need to be adjusted or changed. For example, people often get discharged from the hospital now on dual antiplatelet therapy. We know that combination works to reduce risk but shouldn’t be continued indefinitely—its benefits are there up to about a month or so. After that point, patients should probably be transitioned to a single agent. It’s important for that information to get from the neurology team in the acute setting to the secondary care or a primary care provider afterward. Some of the patient evaluation also may not be completed during the initial hospitalization. The evaluation for atrial fibrillation, for example, can require long-term monitoring of the patient after they leave the hospital. All that information needs to be transmitted to the primary care provider after they leave, and I think that’s part of having an ideal stroke system of care set up.

Q: How would you describe the state of education on stroke care among primary care providers?

Primary care providers know how to manage a lot of the conditions that are so central to the cause of stroke and to preventing stroke recurrence. They’re really the experts at speaking with patients about the use of medications to address their high blood pressure, blood sugar issues, and cholesterol levels. They’re also experts at addressing issues like adherence. They’re good at getting information from patients about adverse effects that they may be having but maybe not sharing with other physicians, like their neurologist, for example. They may be able to help people understand their medications better and adjust their use of those medications. Primary care providers are also the ones that we turn to when we have questions about lifestyle issues: What kind of diet should I have? How can I get enough exercise? They’re ideally positioned to help with a lot of those kinds of questions that are fundamental to people’s health, and not only to their risk of stroke, of course, but also to their risk of cardiac disease or other vascular disease throughout the body. These are things that the primary care physicians can certainly make a major contributions to, for their patients.

There are some things that are specific to stroke care. After stroke, for example, people are at risk of developing depression—about one-third of patients will develop depression after a stroke. This is also something that primary care physicians are attuned to and know to look for. Anxiety can [also] be a big problem. Even posttraumatic stress disorder occurs after an acute event like a stroke. [Then] there are some problems that may be a little bit less familiar to primary care doctors—for example, certain pain syndromes like the frozen shoulder syndrome that some people get when they develop hemiparesis and they can’t move their arm, with the shoulder becoming painfully tight and stiff. That can be an issue that may be less common in the primary care practice. Similarly, central pain syndromes and certain types of stroke leave people with pain in different parts of the body. That can be confusing because one may go looking for alternative explanations of the pain rather than the stroke. For example, with spasticity or spasms of the limbs after a stroke and a paralyzed arm, some people may have pain or jerking movements of the weak limb. These may be things also that the primary care physician may want to turn to a neurologist, a physiatrist, or a rehabilitation specialist for help with. There are things like that, which I think the primary care community would benefit from more education about, at least so that they can recognize those problems in those syndromes and then be able to refer people back for specialty care to specifically manage and address them.

Q: How important is it to have established systems of care in stroke?

[They] have become so important in all that we do. We recognize that when systems fall short, for example, when structural racist systems are in place, they help to facilitate disparities and inequalities in health care. Those are bad systems. They make resources less available to certain groups of people compared with others. Conversely, we can make a choice to make better systems that facilitate medication availability, insurance availability, adherence to medications, and healthy environments...and so forth. What we need to do is not put all the pressure on the individual patient and the physician but create systems that can be facilitated by hospitals and accountable care organizations that make health care easier to provide for all of us.
ZEPOSIA—FOCUSED ON WHAT COUNTS

ZEPOSIA was studied in the largest number of patients with RMS in 2 pivotal head-to-head trials against an active comparator (N=2659) in reducing relapses vs Avonex3.

POWERFUL Efficacy1b
Proven superior in reducing relapses vs Avonex3
Proven superior in reducing GdE and T2 lesions vs Avonex

COMPARABLE Safety Profile vs Avonex in Overall Incidence of Adverse Reactions1c3c
Consistently low discontinuation rates vs Avonex
Comparable rates of serious infections and malignancies vs Avonex

The FIRST AND ONLY S1P With No First-Dose Observation Required1d4.5e
Full Prescribing Information for ZEPOSIA has
NO FIRST-DOSE OBSERVATION required
NO genetic testing required
NO ophthalmic testing required for most patients1f

2659 patients includes all 3 arms of the study: the 0.92-mg dose of ZEPOSIA, the 0.46-mg dose of ZEPOSIA (not approved for maintenance dose), and the 30-µg dose of Avonex.2,3

1bStudy 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 vs 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.2,3

1cAdverse reactions: Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis. Respiratory tract infection, bronchitis, rhinitis. Respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. 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 1.1% vs 0.7% 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 2.0% vs 0.0% for Avonex and at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.1,3

Indication
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.

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

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.
Contraindications: ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome.

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

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (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 ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another SIP receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

- Progressive Multifocal Leuкоencephalopathy (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 SIP 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.
IMPORTANT SAFETY INFORMATION (CONTINUED)

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

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

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

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

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

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

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

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

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

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

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

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

Please see Important Safety Information throughout and Brief Summary of full 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)].

2.2 Dosing Information

Maintenance Dosage

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

Table 1: Dose Titration Regimen

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>Days 1-7</td>
<td>0.23 mg</td>
</tr>
<tr>
<td>Days 8 and thereafter</td>
<td>0.92 mg</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 (MAD) Inhibitor [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

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 (35% 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.

Herpes Viral Infection

In Study 1 and Study 2, herpes 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. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA (see Vaccinations below).

Cryptococcal Infection

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P 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 Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and thus usually leads to death or severe disability. Typical symptoms associated with PML are diverse, with progression 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 S1P 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 immunosuppression. Physicians should closely monitor the patient and consider reducing the dose of ZEPOSIA.

2.4 Vaccinations

No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations should be administered with caution. 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)].

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.

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

5.2 Bradycardia 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 (QTc > 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 pre-existing stable cardiac conditions without clearance from a cardiologist

• Severe untreated sleep apnea

• A resting heart rate less than 55 beats per minute (bpm) at baseline

6 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 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 0.6% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

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, 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 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 From Prior Treatment with 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, when initiating ZEPOSIA.

Initiating treatment with ZEPOSIA after treatment with alentumizumab 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 Atrioventricular Conduction Delays [see Warnings and Precautions (5.2)]
• Liver Injury [see Warnings and Precautions (5.3)]
• Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]
• Severe Increase in Disability 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, hematocrit 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)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ZEPOSIA 0.92 mg (n=382)</th>
<th>30 mcg Intramuscularly Once Weekly (n=385)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper respiratory infectiona</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic transaminase elevationa</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
2 Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.
3 Includes the following terms: alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.
4 Includes hypertension, essential hypertension, and orthostatic hypertension.
5 Dose-dependent reductions in absolute FEV1 and FVC were observed in patients treated with ZEPOSIA [see Warnings and Precautions (5.6)].

Malignancies

Malignancies, such as melanoma, basal cell carcinoma, breast cancer, and seminoma, were reported with ZEPOSIA in the active-controlled trials for ZEPOSIA. An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with ZEPOSIA in active-controlled MS clinical trials.

7 DRUG INTERACTIONS

7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

ZEPOSIA 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 (5.6)].

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

ZEPOSIA 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

ZEPOSIA 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 ZEPOSIA is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with ZEPOSIA should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties [see Warnings and Precautions (5.2)]. If treatment initiation with ZEPOSIA is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought.

7.3 Vaccination

During, and for up to three months after, discontinuation of treatment with ZEPOSIA, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA [see Warnings and Precautions (5.1)].

7.4 Strong CYP2C8 Inhibitors

Co-administration of ZEPOSIA with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod [see Clinical Pharmacology (12.3)], which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.

7.5 Breast Cancer Resistance Protein (BCRP) Inhibitors

Co-administration of ZEPOSIA with BCRP inhibitors increases the exposure of the active metabolites of ozanimod [see Clinical Pharmacology (12.3)], which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with inhibitors of BCRP (e.g., cyclosporine, eltrombopag) is not recommended.

7.6 Strong CYP2C8 Inducers

Co-administration of ZEPOSIA with strong CYP2C8 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod [see Clinical Pharmacology (12.3)], which may decrease the efficacy of ZEPOSIA. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inducers should be avoided.

7.7 Monoamine Oxidase (MAO) Inhibitors

Co-administration of ZEPOSIA with MAO inhibitors may decrease exposure of the active metabolites of ozanimod. In vitro, the 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.

Opioid Drugs

Serious, sometimes fatal reactions have been precipitated with concomitant use of opioid drugs (e.g., meperidine and its derivatives, methadone, or tramadol) and MAOIs, including selective MAO-B inhibitors. Although a small number of patients treated with ZEPOSIA were concomitantly exposed to opioids, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

Serotonergic Drugs

Although a small number of patients treated with ZEPOSIA were concomitantly exposed to serotonergic medications, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

Sympathomimetic Medications

Concomitant use of ZEPOSIA with pseudoephedrine did not potentiate the effects on blood pressure [see Clinical Pharmacology (12.3)]. However, hypertensive crisis has occurred with administration of ZEPOSIA alone [see Warnings and Precautions (5.5)] and hypertensive crisis has been reported with co-administration of other selective and nonselective MAO inhibitors (e.g., rasagline) with sympathomimetic medications.

7.9 Tyramine

MAO in the gastrointestinal tract and liver (primarily type A) protects from exogenous amines (e.g., tyramine). If tyramine were absorbed intact, it could lead to severe hypertension, including hypertensive crisis. Aged, fermented, cured, smoked, and processed foods containing large amounts of exogenous amines (e.g., aged cheese, pickled herring) may cause release of norepinephrine resulting in a rise in blood pressure (tyramine reaction). Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ZEPOSIA [see Warnings and Precautions (5.5)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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.

Data

Animal Data

Oral administration of ozanimod (0.2, 0.5, or 5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/delayed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 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.

Oral administration of ozanimod (0.2, 0.6, or 2.0 mg/kg/day) to female rabbits during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations (modified blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) for adverse effects on pre- and postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

8.2 Lactation

Risk Summary

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 rat when levels higher than those in maternal plasma.
ZEPOSIA® (ozanimod) capsules, for oral use

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

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 hemangioma 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) assays. Metabolite CC112273 was negative in vivo (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vivo 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) of 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, or 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 patient 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)].

Manufactured for: Celgene Corporation

Summit, NJ 07901

Patent: www.celgene.com/therapies

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ZEP_HCP_BSv.001.05 03/2020
Antiamyloid Agent Donanemab’s Early Success Supports Future Regulatory Consideration

By Marco Meglio

AFTER POSITIVE PHASE 2 FINDINGS resulted in breakthrough therapy designation for donanemab, manufacturer Eli Lilly said it will submit a biologics license application for the agent at the end of the year.

Donanemab, an investigational therapy that targets a modified form of amyloid-β called N3pG, is currently being evaluated for safety and efficacy in the pivotal phase 3 TRAILBLAZER-ALZ 2 study (NCT04437511). The double-blind, randomized controlled trial is meant to replicate the findings of the TRAILBLAZER-ALZ study (NCT03367403), in which donanemab was shown to slow Alzheimer disease (AD) progression by 32% as measured by Integrated Alzheimer’s Disease Rating Scale (iADRS) scores.¹

The phase 3 study is currently enrolling and is expected to reach approximately 1500 participants, aged 60 to 85 years, with early symptomatic AD (TABLE). Investigators will continue to use change from baseline on iADRS as the primary endpoint, with secondary endpoints including Mini-Mental State Examination (MMSE), Alzheimer’s Disease Assessment Scale—Cognitive Subscale (ADAS-Cog-13), and Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB) scores, among others.

Results of the phase 2 TRAILBLAZER-ALZ study were published in the New England Journal of Medicine in March 2021 and suggested that treatment with the therapy results in better composite scores for cognition and ability to perform activities of daily living. After 76 weeks of treatment, those treated with donanemab (n = 131) had iADRS scores change by –6.86 points, whereas the placebo group’s (n = 126) changed by –10.06 (difference, 3.20 [95% CI, 0.12-6.27]; P = .04). Equivalent to a 32% difference in slowing decline, the significant observations were identifiable by month 9.²

In June, the FDA granted breakthrough therapy designation to donanemab as a treatment for AD based on results from TRAILBLAZER-ALZ. “Donanemab has the potential to become a very important treatment for Alzheimer’s disease. We were pleased to see not only slowing of cognitive and functional decline, but also very substantial clearance of amyloid plaques and slowing of spread of tau pathology,” Daniel Skovronsky, MD, PhD, chief scientific and medical officer, Lilly Research Laboratories, Eli Lilly, said in a statement at the time of announcement.³

Reductions in the amyloid plaque level were 85.06 centiloids (–84.13 vs 0.93) greater in the donanemab group compared with those on placebo at the end of the study, as well. As early as 6 months, 40% of those treated with donanemab achieved amyloid negativity (defined as an amyloid plaque level < 24.10 centiloids), with 68% achieving this at 18 months. The percentage of participants in the donanemab group who had amyloid-negative status at 24, 52, and 76 weeks was 40.0%, 59.8%, and 67.8%, respectively.²

Despite achievement of statistical significance on the primary endpoint, results for the secondary outcomes of the trial were mixed. Following the conclusion of the trial, investigators observed a difference of –0.36 (95% CI, –0.83 to 0.12) for CDR-SB score, –1.86 (95% CI, –3.63 to –0.09) for ADAS-Cog-13 score, 1.21 (95% CI, –0.77 to 3.20) for Alzheimer’s Disease Cooperative Study–Instrumental Activities of Daily Living Inventory score, and 0.64 (95% CI, –0.40 to 1.67) for MMSE score.

During the double-blind period, at least 1 adverse event (AE) was reported in 90.8% (n = 119) of the donanemab group and 90.4% (113 of 125) of the placebo group. The incidence of amyloid-related cerebral edema or effusion (ARIA-E) was significantly higher in the donanemab group (26.7%) than in the placebo group (0.8%; P < .001). In total, 6.1% of participants who received donanemab had symptomatic ARIA-E compared with 0.8% of those in the placebo group. Most cases of ARIA-E occurred at or by week 12 of the intervention period, with the serious symptomatic cases (n = 2; 1.5%) occurring in the donanemab group. The symptoms resolved in both patients in a mean time of 18 weeks.

In addition to TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2, other clinical trials are assessing the safety and efficacy of donanemab. These include TRAILBLAZER-ALZ’s long-term extension, TRAILBLAZER-EXT (NCT04640077), and another phase 3 trial, TRAILBLAZER-ALZ 3 (NCT05026866), which was announced in July.⁴ TRAILBLAZER-ALZ 3 is a randomized, placebo-controlled study that is in collaboration with Banner Alzheimer’s Institute. As part of the collaboration, Banner will support enrollment of the trial participants with and without the e4 type of the apolipoprotein gene through the Alzheimer’s Prevention Registry’s GeneMatch program.⁵

**TABLE. Phase 3 TRAILBLAZER-ALZ 2 Study**

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diagnosis of early symptomatic Alzheimer disease</td>
<td>• 1:1 to intravenous donanemab or placebo</td>
</tr>
<tr>
<td>• Age 60-85 years</td>
<td></td>
</tr>
<tr>
<td>• MMSE score of 20-28 (inclusive) at baseline</td>
<td></td>
</tr>
<tr>
<td>• Change from baseline on iADRS</td>
<td></td>
</tr>
</tbody>
</table>

iADRS, Integrated Alzheimer’s Disease Rating Scale; MMSE, Mini-Mental State Exam.

For a full list of references, see the article on NeurologyLive.com
Accessible Stroke Care for Diverse Populations: The Montefiore Approach

Years of built-up trust in the community has enabled Montefiore’s Stern Stroke Center physicians to understand more about how stroke affects multicultural communities and to break down existing barriers to care.

By Marco Meglio

IN THE HEART OF THE BRONX, NEW YORK, lies Stern Stroke Center at Montefiore—a leader in stroke services and care with an emphatic mission to provide quality access, raise stroke awareness, and improve poststroke outcomes in diverse populations.

According to a 2020 census report, the Bronx is primarily made up of individuals identifying as Hispanic, accounting for 56% of the population; Black (29%); and White (9%). Of the 1,418,207 people in the borough, 26.4% live below the poverty line, almost double the rate for the state of New York (13%) and more than double that of the United States. Additionally, 33.7% of the population are foreign born, about 1.5 times the rate of New York and more than double the rate of the United States.¹

The stroke-related disparities these individuals face have been well documented. Notable research from Rinaldo et al found that the utilization of mechanical thrombectomy (7% vs 9.8%; \( P < .001 \)) and likelihood of receiving intravenous tissue plasminogen activator (16.2% vs 20.5%; \( P < .001 \)) was lower for Black/Hispanic patients than for White/non-Hispanic patients.²

Understanding the demographics of patients presenting to the stroke center is critical to the approach of care. “The personal challenges are never-ending when it comes to a high-risk community,” Charles C. Esenwa, MD, director at Montefiore’s Comprehensive Stroke Center (Stern Stroke Center), and an assistant professor of neurology at Albert Einstein College of Medicine, told NeurologyLive.³

“That can look different depending on where you are. For example, for inner-city, high-risk communities where we work, these are typically Black and Brown communities that are poor, impoverished, and lower on the circuit of socioeconomic status, and have a lot of social determinants of health,” Esenwa continued. “These social determinants of health are by-products of socioeconomic status and poverty but overlap greatly with race because of the nature of race in the United States.”

Esenwa specializes in vascular neurology with a particular interest in acute stroke management and stroke prevention strategies in high-risk individuals. His research focuses on acute stroke management, stroke risk factors, secondary stroke prevention, and stroke disparities. He believes that its access to a diverse community is part of what gives Montefiore an advantage in tackling these disparities.
“Because we have such a diverse community, we’re able to get to the bottom of these differences: why are there differences in race and are those differences genetic—which is what some people were proposing—or are [they] truly independent of genetic makeup and…more to do with social status,” Esenwa said.

The center treats more than 1400 patients with acute stroke per year, making it the second busiest stroke center in New York state. Many of the stroke experts on staff at the center are multilingual, which helps build communication and trust among those within a culturally different environment.

“Montefiore has a track record of doing good by the community,” Esenwa added. “There’s already a level of trust that’s been built up over the course of years of providing a high level of care to communities that aren’t necessarily getting that high level of care.”

Esenwa, who is from a non-White background, explained that the diversity of the hospital staff also plays a positive role in easing the process for patients. “It’s important to have people that represent the community in the hospital. Our Black, Latinx, gender nonconforming, and [female] patients—are they being represented in the medical staff? When I approach a patient who’s had a stroke [at our center], I can relate to them. That has to do with representation on our teams,” he said.

Accessibility to stroke care at all stages has become more of an issue for these communities in recent years but remains an area of concern overall. Results of research presented at the American Stroke Association (ASA) International Stroke Conference 2021 showed that although endovascular therapy (EVT) utilization has increased across all racial/ethnic groups since the treatment was validated in 2015, disparities are still present. Black patients were 32% less likely to receive EVT before 2015 and remained 17% less likely to receive it from 2015 on.

“Although we deliver state-of-the-art stroke care that includes cutting-edge surgical and interventional procedures, we still make a point…of having the stroke faculty immediately available to patients,” Daniel L. Labovitz, MD, MS, medical director of Montefiore Comprehensive Stroke Center, and an assistant professor at Albert Einstein School of Medicine, told NeurologyLive®.

Labovitz’s research focuses on racial, ethnic, and social disparities in stroke incidence and outcomes, as well as the incidence and determinants of intracerebral hemorrhage and stroke-related epilepsy. He and Esenwa’s most recent research involved the effect of race on composite thrombotic events in patients with COVID-19. Using a multiracial cohort, they found no significant race-specific differences in thrombotic events.

“It’s very clear it’s not a genetic predisposition, it’s a socioeconomic predisposition,” Esenwa said regarding the study, “whether that’s a frontline worker who must go to work because they can’t use Zoom, or it’s because they live with 4 or 5 people in their household and that puts them at risk, or because they live in a dense neighborhood with a lack of resources. Those are the things that put people at a higher risk of dying.”

Again, Esenwa attributes the diverse community as a vehicle to understanding racial disparities and where they stem from, whether that be genetics, a view that has been traditionally imposed, or socioeconomic status, which has been highlighted in recent years. In 2017, Labovitz was an investigator on a study that examined racial/ethnic disparities in hospital arrival times among 1790 patients with acute ischemic stroke who presented to a tertiary-case hospital in the Bronx. The cohort consisted of 338 Caucasians, 662 Hispanics, and 790 African Americans. At the conclusion of the study, a greater proportion of Hispanic and African American women than Caucasian women (74% and 72% vs 59%, respectively) had had delayed hospital arrival times (≥ 3 hours) after the onset of stroke symptoms. However, this racial/ethnic difference was no longer present after adjusting for socioeconomic status.

In addition to access of care, Labovitz noted that individuals’ overall awareness and knowledge of stroke needs improvement. The center has tried reaching out to schools as well as working with community leader Olajide A. Williams, MD, MS. Williams, a professor and chief of staff of the Department of Neurology at Columbia University Vagelos College of Physicians and Surgeons, developed a public health campaign that uses hip hop music to teach children how to identify stroke symptoms. He was able to show that elementary school students are educable about stroke, retain their knowledge well, and may be able to appropriately activate emergency services for acute stroke.

Nearly 30% of US adults younger than 45 years don’t know all 5 of the most common stroke symptoms, according to the ASA. Hispanic adults and adults not born in the United States are about twice as likely to be unaware of any of the common stroke symptoms compared with non-Hispanic White people and those born in the country. “One problem with stroke is that it doesn’t hurt. Heart attacks hurt. You get chest pains, you become uncomfortable, you seek help. Stroke mostly doesn’t hurt. It’s possible for someone to get the symptoms of a stroke and wait for their

“These social determinants of health [that typically Black and Brown communities experience] are by-products of socioeconomic status and poverty, but overlap greatly with race because of the nature of race in the United States.”

—CHARLES C. ESENWA, MD

NeurologyLive.com

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daughter to come home instead of seeking any help because they think it’s going to go away,” Labovitz said.

The center has reached out to individuals within the community to try to raise awareness of and combat these knowledge gaps. Additionally, it provides stroke support groups dedicated to educating patients and their families. Montefiore has also opened its doors to the community for World Stroke Day, a worldwide initiative that takes place on October 29 each year to increase awareness and drive action on stroke prevention.

“We recognize that this is beyond just a one-person issue [and that it is] a population-level issue,” Esenwa said. “We work closely with organizations like the American Heart Association to get the word out about stroke recognition and using BE FAST.” BE FAST—Balance, Eyes, Face Drooping, Arm Weakness, Speech Difficulty, and Time to call 911—helps individuals remember the signs of stroke and what to do if someone is experiencing them.

Stroke recognition, especially among the younger population, is another area on which the center has concentrated significantly. Usually considered as something that occurs in older individuals, stroke has become more prevalent among younger adults, with literature suggesting that about 10% to 15% of strokes occur in those aged 18 to 50 years. A county-by-county analysis found that between 2010 and 2016, strokes among middle-aged people had increased 3 times as much as strokes in people over the age of 64 years. Notably, these statistics were not confined to the “Stroke Belt,” a swath of the southeastern United States where stroke rates are between 2 and 4 times the national average.

Esenwa was a senior author of a retrospective study published earlier this year that gained insights into the presence or absence of cardiovascular risk factors in cases of cryptogenic stroke in adults aged 18 to 49 years. These patients had higher rates of hypertension, intracranial atherosclerosis, and diabetes mellitus. Upon admission, they also demonstrated higher glucose HbA1c levels, blood pressure, and cholesterol compared with patients with cardioembolic acute ischemic stroke. The investigators concluded that half of young patients with cryptogenic stroke fit the risk factor phenotype of small and large vessel strokes.

“We came up with this notion that it’s not the rare stuff you should be looking for in the youth, it’s the typical stuff that you should be looking for,” Esenwa said about the data. “Just look for the uncontrolled version of the typical stuff. That understanding shifts the narrow view of stroke in the young to a broader view that’s inclusive of communities like ours. It also opens doors to look at it from a preventive standpoint.”

Looking forward, the center remains committed to its research efforts and goals of understanding more about how social determinants of health affect multicultural communities. According to Esenwa, once this information is more regularly recorded, Montefiore can then implement additional programs to treat these high-risk individuals.

“We pride ourselves on being just like everybody else in the sense that we are held to very strict standards,” Labovitz concluded. “The stroke community has worked incredibly hard over the past 2 decades to share best practices, establish standards of care, and set benchmarks for rapid delivery of care. And Montefiore is right in the thick of it. What’s special about us, though, is that we deliver this state-of-the-art care in an incredibly humane and kind way.”

REFERENCES

EXCESSIVE DAYTIME SLEEPINESS (EDS), demonstrated by episodes of daytime sleep or an uncontrollable need to sleep, is highly prevalent, with recent articles showing it affects about 20% of the world population. Clinicians in all fields, and frequently neurologists, will encounter patients with EDS. The differential diagnosis for EDS can be organized into primary and secondary causes.

The International Classification of Sleep Disorders—Third Edition includes primary and secondary causes of EDS, referred to as hypersomnias, under the Central Disorders of Hypersomnolence category. Secondary causes are more varied and more common than primary causes and must be excluded before a diagnosis of a primary hypersomnia can be made. This article will review the secondary causes of EDS to help providers determine when an evaluation for primary causes of EDS is warranted. This is followed by a discussion of the primary hypersomnias, addressing both diagnostic and treatment paradigms for the central disorders of hypersomnolence.

Secondary Hypersomnias

Insufficient Sleep Syndrome
An estimated 27% of Americans sleep fewer than 8 hours per night, and 18% sleep fewer than 6 hours per night, leading to a large sleep-deprived population. Although individuals sleeping 6 to 7 hours per night are likely to exhibit some degree of daytime sleepiness, 6 hours of sleep per night is the generally accepted minimum below which a primary hypersomnia would not be diagnosable because of the presence of marked sleep deprivation.

In addition to short sleep, poor-quality sleep related to various factors, such as a sleep environment that is not restful, chronic pain, and shift work, can contribute to EDS and should be treated prior to pursuing a diagnosis of a central disorder of hypersomnolence. Evaluation methods for insufficient sleep include a comprehensive sleep history, sleep diaries, and, if necessary, actigraphy.

Hypersomnia From a Medication or Substance
Medications and substances can cause sleepiness directly and indirectly. Patients with insomnia who are prescribed long-acting soporific medications, such as trazodone and clonazepam, can present with iatrogenic EDS. This should not be confused for endogenous sleepiness, as the presenting complaint is difficulty sleeping. Although narcolepsy, the most common primary hypersomnia, is well known to be associated with disrupted nighttime sleep, severe sleep initiation insomnia requiring pharmacotherapy to induce sleep is less likely to be a feature of narcolepsy, and the sleepiness must predate the initiation of hypnotic medications for a primary hypersomnia to be considered.

A comprehensive review of all sedating medications is beyond the scope of this article, but drugs from many classes of medication should be considered as potential causes of EDS, including benzodiazepines and barbiturates, first-generation antihistamines, antipsychotics, antiemetics, antidepressants, dopamine agonists, and some antihypertensives. Opiates, by contrast, are most sedating with short-term use, and patients who use chronic, prescription opiates may experience less sleepiness, although some (eg, methadone) can be persistently sedating. Substances such as alcohol, cannabis, and herbal supplements should also be screened as part of an evaluation of EDS. Stimulant withdrawal is a cause of acute EDS but is not expected to cause chronic EDS. Sedating drugs should be reduced and eliminated when possible prior to pursuing a diagnosis of a primary hypersomnia.

Hypersomnia Due to a Medical Disorder/Associated With a Psychiatric Disorder
Several medical conditions involving the cardiovascular, nervous system, and endocrine systems are associated with sleepiness. Conditions such as sleep apnea, obesity, acid reflux, hypothyroidism, and depression are frequently associated with EDS.

Patient Evaluation for Excessive Daytime Sleepiness

By Lauren Chamberlain, DO*; and Andrew Spector, MD**

*PGY-4, Child Neurology, Duke University Hospital
**Vice Chair, Inclusion, Diversity, and Empowerment; Associate Professor of Neurology; Duke University School of Medicine
respiratory, hematologic, and neurologic systems can cause excessive sleepiness, such as coronary artery disease, obstructive sleep apnea, and sickle cell anemia, as well as psychiatric diseases.\(^6\)\(^{10}\)

Frequently, the medical conditions that lead to EDS are chronic diseases that affect vital organ function or cause pain, leading to poor sleep and, in turn, EDS. If any of these disorders is suspected, the treatment for the sleepiness is management of the underlying condition.

Stimulants can be offered if deemed safe and necessary once the patient is medically optimized.

Other Sleep Disorders
EDS is a common symptom in most sleep disorders.\(^1\) As part of any evaluation for EDS, a comprehensive sleep history should be performed to screen for sleep-related breathing disorders (eg, obstructive or central sleep apnea), circadian rhythm sleep-wake disorders (eg, delayed sleep-wake phase disorder), and sleep-related movement disorders (eg, periodic limb movement disorder). Other sleep disorders must be adequately treated before an evaluation for a primary hypersomnia can occur.

Primary Hypersomnias

Narcolepsy
Narcolepsy is divided into type 1 and type 2, which is equivalent to with and without cataplexy, respectively.\(^2\) Cataplexy is the sudden and brief loss of muscle tone in response to an emotional trigger, most commonly laughter. Although narcolepsy is associated with 4 classic symptoms other than cataplexy, the only one required for diagnosis is EDS. The other symptoms that are present in varying frequencies are hypnagogic and hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep. One conceptualization of narcolepsy is a disease of unstable REM sleep with REM imagery and REM paralysis bleeding over into wakefulness.

Narcolepsy type 1 is caused by orexin deficiency.\(^3\) The orexin system involves 2 small neuropeptides (orexin A and orexin B) that are responsible for exciting target neurons throughout the cortex.\(^4\) The absence of orexin disrupts frontal and limbic-diencephalic systems, and the brainstem. Narcolepsy type 1 is thought to be an autoimmune process triggered by genetics and environmental factors.\(^5\) There is a known association with human leukocyte antigen (HLA)-DQB1*0602. The etiology of narcolepsy type 2 is less clear, as low orexin and HLA typing are not as strongly associated with type 2 as they are with type 1.

Idiopathic Hypersomnia
Frequently misconceived as a “wastebasket diagnosis” or a diagnosis of exclusion because of its nomenclature, idiopathic hypersomnia (IH) is a specifically defined and severely debilitating condition.\(^1\) The hallmark symptom of IH is profound, unquenchable sleepiness, often leading to patients sleeping more than 10 hours—and sometimes much more than 10 hours—per day.\(^1\) Furthermore, patients often identify severe difficulty awakening from sleep with extreme sleep inertia, also known as sleep drunkenness. Sleep inertia is the sensation of mental fogginess and desire to return to sleep that occurs upon attempting to awaken. Patients with IH tend to get no relief from naps, whereas patients with narcolepsy tend to feel better after even brief naps. Although sleep-related hallucinations and sleep paralysis can occur in IH, these are not considered classic symptoms. The presence of cataplexy would rule out IH, as it is seen only in narcolepsy.

Kleine-Levin Syndrome
An extremely rare condition marked by recurrent periods of profound hypersomnolence alternating with normal sleep-wake behavior is Kleine-Levin syndrome.\(^1\) Episodes of hypersomnolence last up to 5 weeks and then remit, recurring at least twice per year. During the attacks, patients exhibit at least 1 of the following symptoms: cognitive dysfunction, altered perception, eating disorders, and disinhibition. The natural history of the condition is progressive resolution of symptoms over a median of 14 years.

Diagnostic Tests
After ruling out inadequate sleep, medications and substance use, and medical conditions that cause EDS, it is necessary to perform polysomnography to rule out other sleep disorders before making a diagnosis of a primary hypersomnia. Polysomnography will determine the patient’s apnea-hypopnea index (normal, <5/hour). It will also evaluate for periodic limb movements of sleep (normal, <15/hour). If either of these is abnormal, treatment for sleep apnea and periodic limb movement disorder can be attempted prior to further evaluation for a central disorder of hypersomnolence.

If the sleep history does not suggest sleep apnea or excessive limb movements as the cause of the sleepiness, the polysomnogram should be ordered in conjunction with a multiple sleep latency test (MSLT). The polysomnogram will be performed first, followed by the MSLT if the polysomnogram reveals no significant abnormalities. Sleep laboratories have protocols that determine whether an MSLT will be performed following a polysomnogram. Therefore, the referring provider can order both tests together prior to ruling out sleep apnea because the MSLT will be canceled if another sleep disorder is detected. If no other sleep disorder is detected, though, an MSLT will provide valuable diagnostic information about the central disorders of hypersomnolence.

MSLT includes 5 nap opportunities wherein the patient attempts to fall asleep within 20 minutes. If sleep occurs, it can continue for 15 minutes before being interrupted by the technologist. The 2 principal measurements are sleep latency (eg, how long it took to fall asleep) in each nap, which is averaged to determine the mean sleep latency, and the presence of stage REM sleep, referred to as a sleep-onset REM period (SOREMP). The population-based normal mean sleep latency is greater than 10 minutes.\(^13\)\(^14\)
MANAGE-PD allows you to:

- Inform decision making by evaluating motor complications, functional impact, adverse events, and non-motor symptoms
- Determine which patients with PD may be adequately controlled on their current treatment regimen versus those that may require a change to their treatment, including evaluation for device-aided therapy

MANAGE-PD is a collaborative research and development effort between AbbVie Inc. Medical Affairs and Health Economics and Outcomes Research, the Parkinson’s Foundation and an international panel of Movement Disorder Specialists

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US Medical Affairs
Pathological sleepiness is identified by mean sleep latencies less than 8 minutes (8- to 10-minute sleep latencies are borderline abnormal and should be interpreted in the clinical context). In cases of pathological sleepiness, the presence of 2 or more SOREMPs is consistent with narcolepsy, whereas 0 to 1 SOREMP is labeled IH. Studies have shown that the presence of 2 or more SOREMPs with a mean latency of less than 5 minutes had a 97% specificity for the diagnosis of narcolepsy. Unfortunately, the test-retest reliability of MSLT is disturbingly low, and a change in diagnosis from one MSLT to the next occurred in 53% of patients in 1 cohort with EDS.

It is also possible to diagnose narcolepsy by testing orexin levels in the cerebrospinal fluid (CSF). A low CSF orexin A level, defined as less than 110 pg/mL, replaces the MSLT as a diagnostic criterion for narcolepsy. However, it is typically unnecessary to perform CSF testing, as the presence of cataplexy and a positive MSLT are sufficient for the diagnosis. Moreover, narcolepsy without cataplexy is not regularly associated with low CSF orexin, so CSF testing would not be valuable for this population.

Treatment

The treatment of primary hypersonias is symptomatic. There are no disease-modifying therapies available. The traditional stimulants (eg, methylphenidate, amphetamines) and wakefulness promoters (eg, modafinil, armodafinil, solriamfetol) increase dopamine and norepinephrine, whereas the novel drug pitolisant is an inverse agonist at the H₁ histamine receptor. Sodium oxybate, and combination calcium, magnesium, potassium, and sodium oxybates also function to improve wakefulness but do so by enhancing sleep as opposed to directly augmenting arousal pathways. Of these, only calcium, magnesium, potassium, and sodium oxybates (Xywav; Jazz) is labeled for IH, whereas the wakefulness promoters, pitolisant, and both oxybate medications are approved for narcolepsy. Additional treatments for cataplexy are also available.

Effective treatment of primary hypersonias includes navigating the adverse effects of these medications. Traditional stimulants are associated with increases in heart rate and blood pressure level, anorexia, insomnia, and anxiety. Wakefulness promoters may cause headaches, psychiatric disturbances, and Stevens-Johnson syndrome. Adverse effects of pitolisant include insomnia, headaches, and nausea. Oxybate medications, although highly effective, can be difficult for many patients to tolerate because of depression, anxiety, psychosis, and nausea. They also can cause respiratory depression, so they cannot be used with other respiratory-suppressing medications.

Nonpharmacological treatment for primary hypersonias, particularly narcolepsy, includes planned daytime naps, low-carbohydrate diets, and strict sleep hygiene. IH tends not to respond as well to nonpharmacological interventions.

Emerging data support the use of nontraditional medications, such as clarithromycin and flumazenil for IH. Several drugs remain in development, including extended-release oxybate, orexin replacement and orexin receptor agonists, reboxetine (a selective norepinephrine reuptake inhibitor), and a combination pill with modafinil and flecainide, an astrogial connexin inhibitor.

Summary

Patients presenting with EDS can be conceptualized as having either a primary or secondary hypersonia. Secondary causes, such as insufficient sleep, medical or psychiatric disorders, and medications and substances, should be evaluated and treated first. If EDS persists following optimization of each of these, a primary hypersonia should be considered. Polysomnography with MSLT is the test of choice for evaluating primary hypersonias, although MSLT is notoriously unreliable.

The algorithm in the FIGURE should be helpful with this initial evaluation of a patient with EDS. After a clinical diagnosis of a primary hypersonia is made, many pharmacological and nonpharmacological treatments can provide patients with a markedly improved quality of life.

For a full list of references, see the article on NeurologyLive.com.
A New Approach to Protein Misfolding in Parkinson Disease

By Manolo Bellotto, PhD
President and general manager, Gain Therapeutics

Parkinson Disease (PD) is a progressive neurodegenerative disorder with an estimated lifetime risk of 3% to 4%. It impacts more than 1 million people in the United States, making it the second largest neurodegenerative disease here after Alzheimer disease. In addition to symptoms such as tremor, bradykinesia, rigidity, and OFF time, patients with PD also suffer from a range of nonmotor indications including psychosis and dementia. PD manifestations have been identified for more than 200 years, yet its mechanisms and pathogenesis have still not yet been fully described. While current therapies provide relief for some symptoms, they do not influence the progression of the disease.

However, clinical trials investigating potential disease-modifying treatments for PD, focusing on patients with specific gene mutations, are under way. Among the most common risk factors for PD is the presence of mutations in the glucocerebrosidase gene (GBA1), which encodes for the lysosomal enzyme beta-glucocerebrosidase (GCase). This risk factor was discovered during a clinical study of patients with Gaucher disease (GD), a rare lysosomal storage disorder. Over time, researchers have acknowledged that mutations in the GBA1 gene are more prominent than in any other implicated genes within the PD population, including dardarin (leucine-rich repeat kinase 2 [LRKK2]), α-synuclein (SNCA), and parkin (PARKIN2).

Limitations of Current Therapies
Treatments of PD using available drugs have positive symptomatic effects; however, no neuroprotective therapies are available to halt or even slow PD’s progression. Treatments include drugs, surgeries, or combinations thereof, and notably, many therapies must be adjusted throughout the course of the disease: Some common ones, including levodopa, lose effectiveness over time and will not have an impact on motor problems caused by, for example, low acetylcholine levels in other pathways. Furthermore, mainstream treatments such as enzyme replacement therapy (ERT) or gene therapy target only a small portion of the patient population, because they are severely limited in their ability to penetrate the blood-brain barrier (BBB). PD treatment usually begins when symptoms start to impair function or result in social embarrassment.

The Intersection of GD, PD, and GBA1
A new research area is leveraging disease pathways of GD to find a more effective treatment for PD. As GD research progresses, scientists are discovering stronger links between GD and PD.
yet much remains to be learned about how and why these 2 diseases are related. Hopefully, important insights into mutual therapeutic options will develop. GD is caused by mutations in the GBA gene, which also can lead to reduced levels of GCase activity with the consequent accumulation of a primary substrate, glucosylceramide.¹

Treatments for GD have been developed that increase visceral GCase levels and decrease lipid storage, although these treatments do not yet address the neurological defects associated with impaired GCase enzyme. Mouse models and induced pluripotent stem cell–derived models have improved our understanding of the GCase function and consequences of its deficiency. These models have been used to test novel therapies, including chaperone proteins (molecular chaperones that assist other proteins to fold properly), histone deacetylase inhibitors, and gene therapy approaches, all of which enhance GCase levels and could prove efficacious in treating PD.²

Patients with GD, as well as heterozygous GD carriers, are at increased risk of developing PD and dementia with Lewy bodies. An inverse relationship between GCase and α-synuclein levels has been observed, and even patients with sporadic PD have decreased GCase.³

Patients with GBA1-associated PD compose about 10% of total PD patient population,⁴ and while they are indistinguishable from other patients with PD, their disease may progress more rapidly with heightened severity. Research has shown that the onset of motor impairment among GBA1 mutation carriers who have PD occurs 1.7 to 6.0 years sooner than in those patients with PD who don't have the mutations. Further, about 15% of patients with GBA1-associated PD exhibit severe clinical features; the features of the other 85% are usually moderate to severe. Finally, among patients who develop PD when less than 50 years, GBA1 mutation carriers tend to develop clinical symptoms earlier than those who do not carry the mutation.

GBA1 and Protein Misfolding: An Underlying Biological Issue
Proteins are the primary building block of the human body, and they must maintain their precise 3D structure to ensure normal functionality. The physical process by which a protein chain is translated into its native structure, taking shape from its building blocks, and becomes a biological function as a 3D structure is called protein folding. Protein misfolding is a characteristic of PD and many other neurodegenerative diseases: Misfolded protein aggregation causes toxicities—including endoplasmic reticulum (ER) stress from an accumulation of misfolded proteins within the ER, or cellular toxicity due to an accumulation of the enzyme's substrate within the cells—resulting in cellular death and proteostatic disturbances. In PD, GBA1 mutations result in the misfolding and subsequent dysfunction of GCase, which leads to the toxic accumulation of synuclein and neuronal cell death. Proteins misfold for many reasons, including genetic mutations and stress-induced molecular changes associated with inflammation or aging.

If misfolded proteins can be guided back into their normal structural shape, their function can be restored and catalytic reactions can be reignited. This could also help diminish ER stress by reducing the presence of misfolded proteins in the lumen of ER and eliminating the toxic substrate buildup that causes disease. The current standard of care for diseases characterized by misfolded proteins is to supply new, functional enzymes through ERT or gene therapy. Unfortunately, though, these methods have significant limitations for treating the diseases' neurological symptoms, because replaced enzymes cannot cross the BBB.

Allosteric Binding Sites to Guide Enzymes Back into Their Proper Shape

Binding sites are important locations on enzymes or proteins on which incoming small molecules can attach and create important biochemical reactions. Further, an enzyme can have drugs bind to either its unique active site or nonactive (allosteric) sites. Active sites are generally cavities that exist in the folded state; drugs can be designed to enter them and ‘lock things down’ in place. The problem for an enzyme like a lysosomal hydrolase is that the active site is where most of the chemical activity happens. Therefore, locking down the structure by binding in the active site might make an enzyme more stable but also may render the site less reactive or productive.

Since most pharmacologic chaperones bind to the active site to stabilize the target enzyme, they must compete with other high concentrations of substrate, generating problems in the potency level achieved. Alternatively, by having a compound bind to an allosteric site, the enzyme’s active site remains available to catalyze substrates (FIGURE 1).

FIGURE 1. Allosteric and Active Binding Sites.

Allosteric binding sites are away from the active site and employ the idea of locking the protein in the folded state by binding within a cavity that occurs only in the folded state.

Unfortunately, the enzyme’s allosteric sites are often unknown, making drug modulatory effects hard to predict. In fact, most
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Allosteric modulators were discovered serendipitously—for example, through high-throughput screening during lead identification—but the process is still largely inefficient.

In response, Gain Therapeutics, a drug discovery company based in Bethesda, Maryland, has exclusively in-licensed a patented, site-directed enzyme enhancement therapy platform developed by Gain’s chief scientific officer, Xavier Barril, PhD, in the Barril Lab at the University of Barcelona. The platform rapidly “finds” previously unidentified allosteric binding sites and can predict such a site’s druggability by using libraries that include multimillion compounds; this is in contrast to the current phenotypic cell-based screenings that are intensely laborious. For the first time, these sites can be targeted for therapeutic benefit to correct enzyme misfolding, to restore function, and to eliminate the subsequent toxic substrate buildup that causes disease and malfunction.

Selected compounds called Structurally Targeted Allosteric Regulators (STARs) offer a variety of advantages over traditional therapies; these advantages include streamlined oral dosing, improved delivery to dense tissues such as bone and cartilage, improved delivery across the BBB, and synergy with current gene therapy and ERT approaches.

**Allosteric Regulators Open New Treatment Approach for PD**

**FIGURE 2. In Vivo Rat Model**

GT-02287 showed the tendency to:
- Increased TH (dopamine synthesis biomarker)
- Decrease alpha synuclein
- Improve locomotor activity vs. vehicle treated rats

Selected compounds called Structurally Targeted Allosteric Regulators (STARs) offer a variety of advantages over traditional therapies; these advantages include streamlined oral dosing, improved delivery to dense tissues such as bone and cartilage, improved delivery across the BBB, and synergy with current gene therapy and ERT approaches.

Congress on Parkinson’s Disease and Related Disorders in May 2021. These compounds represent a new approach for direct treatment of GBA1-associated PD by guiding misfolded forms of the GCase enzyme to their proper shape and restoring enzymatic activity. In addition, these compounds decrease both phosphorylated and aggregated α-synuclein levels in vitro and in vivo. When delivered orally, GT-02329 successfully penetrated the BBB and enhanced GCase activity and protein levels in the striatum of wild-type mice, while GT-02287 reduced α-synuclein accumulation in both cell culture and rat models of PD. GT-02287 also improved motor activity in rats treated with rotenone, a model of PD that reproduces certain features of the human disease (FIGURE 2). Importantly, these compounds reversed the neurodegenerative process observed in a PD in vivo model.7

**Conclusions**

PD treatments to date are limited to managing symptoms; they do not affect patients’ inexorable decline. Previously, many promising treatments for PD have ultimately resulted in untenable adverse effects or in failure to cross the BBB. The evolving area of protein folding offers an opportunity to slow or reverse the neurodegenerative process and create improved quality of life for patients. Within the protein folding area, promise is seen with the 2 STAR candidates that could potentially help Parkinson’s patients who have GBA1 gene mutations as well as patients whose GCase protein is misfolded due to inflammation or aging cellular processes. These candidates could enter human clinical studies as soon as 2022, offering some hope for patients who continue to endure these diseases.

**REFERENCES**


Encouraging results of studies with 2 STAR drug candidates (GT-02287 and GT-02329) were presented at the XXVI World
RESEARCH AWARDS

Muscular Dystrophy Canada Announces Funding for Newborn SMA Screening

In July, Muscular Dystrophy Canada (MDC) announced funding for newborn screening projects in spinal muscular atrophy (SMA), the leading genetic cause of infant death. Funding is being provided in part by Novartis Pharmaceuticals Canada, Inc, with more than $700,000 awarded to projects in 3 provinces: Alberta, Manitoba, and Quebec. Ontario is currently the only Canadian province screening for SMA, but the multiyear project anticipates investments totaling $2 million, working toward adding SMA to all provincial and territorial newborn screening panels. Early diagnosis and treatment of SMA is crucial to stop irreversible motor neuron loss and improve patient outcomes. Prior to funding allocation, MDC and Novartis conducted a readiness assessment, with proposals assessed by an independent international peer review committee.

NRG Therapeutics Receives $500K Grant From the MJFF

NRG Therapeutics announced in July that it had been awarded a grant totaling $500,000 from the Michael J. Fox Foundation for Parkinson’s Research (MJFF). The funds will support NRG Therapeutics’ efforts in drug discovery and developing a novel treatment for Parkinson disease (PD). Experts will focus specifically on innovations within the field of mitochondrial biology, hoping to render a treatment via the mitochondrial permeability transition pore (mPTP) in brain cells. “We are delighted to have received funding from MJFF to help us advance our understanding of the molecular target for our mPTP inhibitors,” Neil Miller, PhD, CEO, NRG Therapeutics, said in a statement. “Despite recent successes, truly disease-modifying treatments for PD and other neurodegenerative diseases remain the holy grail.” NRG’s lead drug candidate was identified through phenotypic screening, the molecular targets of which are anticipated to be identified via experiments using a chemo-proteomic platform.

Washington University in St Louis Receives Funding to Study Brain Recovery Post Stroke

A team of investigators at Washington University in St Louis have received a $3.12 million grant from the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, to study neurovascular recovery following an ischemic stroke. The multidisciplinary team includes investigators with expertise in electrical and biomedical engineering, as well as in neurology. The prototype system the team developed combines 2-photon fluorescence microscopy with photo-acoustic microscopy to visualize blood oxygen delivery as it responds to neuronal activity during stroke recovery. This system will then be paired with a photonic sensor resonator with whispering-gallery mode, a transparent version of which will detect the smallest ultrasound signals. It was developed by Lan Yang, PhD, MS, the Edwin H. & Florence G. Skinner Professor in the Preston M. Green Department of Electrical & Systems Engineering.

$1.25 Million NIH Grant Will Fund Neurogenerative Disease Research

The Lewis Katz School of Medicine at Temple University has received a 5-year, $1.25 million grant from the National Institutes of Health’s National Institute of Neurological Disorders and Stroke to fund research efforts in the neurogenerative disease space. Investigators will aim to evaluate the presence of a unique molecular mechanism in association with declining neuronal function, with specific focus on axon degeneration. “Our hope is that through this work we will be able to identify novel proteins involved in axon survival,” said Gareth Thomas, PhD, in a statement. “Doing so may reveal new therapeutic targets that could guide the development of drugs to ameliorate neurodegenerative conditions.” Thomas is principal investigator on the grant; an associate professor of neural sciences and biomedical education and data science, Katz School of Medicine; and an associate professor at Shriners Hospitals Pediatric Research Center.

AT THE HELM

Cognoptix Announces New Scientific Advisory Board Member, Marwan Sabbagh, MD

Marwan Sabbagh, MD, was named the newest member of the Scientific Advisory Board at Cognoptix in August. Prior to his role at Cognoptix, Sabbagh served as the director of the Alzheimer’s and Memory Disorders Division and professor of neurology at the Barrow Neurological Institute in Phoenix, Arizona. While on the Scientific Advisory Board, Sabbagh will apply his expertise in directing company goals, specifically in receiving FDA approval for the Sapphire II system, a point-of-care device that can detect 8-amyloid in the lens of the eye, helping to identify and diagnose patients with early-stage Alzheimer disease (AD). Sabbagh brings unique perspective to the Cognoptix team; he authored “Alzheimer’s Disease Drug Development Pipeline: 2020,” demonstrating an understanding of the early AD therapeutics market and the present opportunities available for the Sapphire II System.
DYSFUNCTION. DESTRUCTION. NEURONAL DEATH IN ALS.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) DISEASE PATHWAYS: EMERGING INSIGHTS

Advances in understanding neuronal survival and degeneration underscore the central role that the endoplasmic reticulum (ER) and mitochondria play in ALS.1-4

1. In ALS, ER stress and dysfunction, in combination with abnormal DNA transcription, lead to misfolded proteins and accumulating protein aggregates, worsening ER stress, and neuronal death.2,3,5,6

2. In ALS, mitochondrial dysfunction and release of cytochrome C, along with an imbalance of pro- and antiapoptotic factor production, trigger the mitochondrial apoptotic pathway, leading directly to neuronal death.2


Scan this QR code or visit ALS-Insights.com/NL to explore the importance of these and other converging pathways in ALS.