CLIMBING THE CAREER LADDER
Profiles of 8 healthcare executives

Technology
Telehealth deals
Oncology
Indication withdrawals
Population Health
Income volatility
Chronic Disease
Specialists and value-based care
Industry Analysis
Insurance newcomers
INDICATION
PONVORY™ is a sphingosine 1-phosphate receptor modulator 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 (continued)
Risk of Infections (continued)
increase the susceptibility to infections. Life-threatening and rare fatal infections have been reported in association with other sphingosine 1-phosphate (S1P) receptor modulators. Before initiating treatment with PONVORY™, results from a recent complete blood count and rare fatal infections have been reported in association with other sphingosine 1-phosphate (S1P) receptor modulators. Before initiating treatment with PONVORY™, results from a recent complete blood count including lymphocyte count should be reviewed.

Herpes Viral Infections
Cases of herpes viral infection have been reported in the development program of PONVORY™; herpes simplex encephalitis and varicella zoster meningitis have been reported with other S1P receptor modulators. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination should be tested for antibodies to VZV prior to initiating PONVORY™.

Cryptococcal Infections
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with other 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. PONVORY™ treatment should be suspended until a cryptococcal infection is confirmed by appropriate treatment should be initiated.

PMV has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

PONVORY™ was proven superior at reducing relapses and lesions vs Aubagio® in a study lasting ~2 years

HELPING CONTROL MS TODAY

MAKING PLANS FOR TOMORROW

Not an actual patient.
PERIPHERAL LYMPHOCYTE COUNT TO 30-40% OF BASELINE

RISK OF INFECTIONS

WARNINGS AND PRECAUTIONS

• Have presence of Mobitz Type II second-degree,
• In the last 6 months experienced myocardial infarction,
PONVORY™ is contraindicated in patients who:

CONTRAINDICATIONS

IMPORTANT SAFETY INFORMATION

active secondary progressive disease, in adults.

forms of multiple sclerosis (MS), to include clinically

PONVORY™ is a sphingosine 1-phosphate receptor

INDICATION

syndrome, or sino-atrial block, unless patient has a
• third-degree atrioventricular (AV) block, or sick sinus
• decompensated heart failure requiring hospitalization,
• unstable angina, stroke, transient ischemic attack (TIA),
development program of PONVORY™; herpes simplex

CRYPTOCOCCAL INFECTIONS

Cases of fatal cryptococcal meningitis (CM) and

VZV prior to initiating PONVORY™.

course of vaccination should be tested for antibodies to

varicella (chickenpox) or without documentation of a full

Herpes Viral Infections

Cases of herpes viral infection have been reported in the

important to note that patients with a history of

immunocompromising conditions (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects.

Progressive Multifocal Leukoencephalopathy (PML)

suggestive of PML. MRI findings may be apparent

before clinical signs or symptoms. If PML is suspected,
treatment with PONVORY™ should be suspended until

If PML is confirmed, treatment with PONVORY™ should be discontinued.

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

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported in patients treated with a

SIP receptor modulator 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 magnetic
resonance imaging (MRI) findings that may be
WARNINGS AND PRECAUTIONS (continued)

Vaccinations

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

No clinical data are available on the efficacy and safety of vaccinations in patients taking PONVORY™. Vaccinations may be less effective if administered during PONVORY™ treatment. If live attenuated vaccines are required, administer at least 1 month prior to initiation of PONVORY™. Avoid the use of live attenuated vaccines during and for 1 to 2 weeks after treatment of PONVORY™.

Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of PONVORY™ treatment results in a transient decrease in heart rate and atrioventricular (AV) conduction delays, an up-titration scheme must be used to reach the maintenance dosage of PONVORY™ (20 mg).

Reduction in Heart Rate

Initiation of PONVORY™ may result in a transient decrease in heart rate. After the first titration dose of PONVORY™, the decrease in heart rate typically begins within an hour and reaches its nadir within 2–4 hours. The heart rate typically recovers to baseline levels 4–5 hours after administration.

Atrioventricular Conduction Delays

Initiation of PONVORY™ treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. If treatment with PONVORY™ is considered, advice from a cardiologist should be sought for individuals:

- With significant QT prolongation (QTc greater than 500 msec).
- With atrial flutter fibrillation or arrhythmia treated with Class Ia or Class III anti-arrhythmic drugs.
- With unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), or uncontrolled hypertension.
- With a history of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block.

Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present. For patients taking other drugs that decrease heart rate, treatment with PONVORY™ should generally not be initiated without consultation from a cardiologist because of the potential effect on heart rate.

Atrioventricular Conduction Delays (continued)

In all patients, a dose titration is recommended for initiation of PONVORY™ treatment to help reduce cardiac effects.

Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV₁) and reductions in diffusion lung capacity for carbon monoxide (DLCO) were observed in PONVORY™-treated patients mostly occurring in the first month after treatment initiation. Spirometric evaluation of respiratory function should be performed during therapy with PONVORY™ if clinically indicated.

Liver Injury

Elevations of transaminases may occur in PONVORY™-treated patients. Obtain transaminase and bilirubin levels, if not recently available (i.e., within last 6 months) before initiation of PONVORY™ therapy.

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

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). PONVORY™ is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively).

Increased Blood Pressure

PONVORY™-treated patients had an average increase of 2.9 mmHg in systolic blood pressure and 2.8 mmHg in diastolic blood pressure. Blood pressure should be monitored during treatment with PONVORY™ and managed appropriately.

Cutaneous Malignancies

Cases of basal cell carcinoma and other skin malignancies have been reported in patients treated with SIP receptor modulators, including PONVORY™. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended in patients taking PONVORY™.

Fetal Risk

Based on animal studies, PONVORY™ may cause fetal harm. Because it takes approximately 1 week to eliminate PONVORY™ from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 1 week after stopping PONVORY™ treatment.

Macular Edema

SIP receptor modulators, including PONVORY™, have been associated with an increased risk of macular edema. An ophthalmic evaluation of the fundus,
**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Macular Edema (continued)**

including the macula, is recommended in all patients before starting treatment and again at any time if a patient reports any change in vision while on PONVORY™ therapy. Continuation of therapy in patients with macular edema has not been evaluated.

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

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during therapy with S1P receptor modulators, including PONVORY™. Therefore, these patients should have regular follow-up examinations of the fundus, including the macula, during treatment with PONVORY™.

**Posterior Reversible Encephalopathy Syndrome**

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1-phosphate (SIP) receptor modulator. Such events have not been reported for PONVORY™-treated patients in the development program. However, should a PONVORY™-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, PONVORY™ should be discontinued.

**Unintended Additive Immunosuppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Therapies**

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation, when initiating PONVORY™. Initiating treatment with PONVORY™ after treatment with alemtuzumab is not recommended.

**Severe Increase in Disability After Stopping PONVORY™**

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

**Immune System Effects After Stopping PONVORY™**

After stopping PONVORY™ therapy, ponesimod remains in the blood for up to 1 week. Starting other therapies during this interval will result in concomitant exposure to ponesimod.

**Immune System Effects After Stopping PONVORY™ (continued)**

Lymphocyte counts returned to the normal range in 90% of patients within 1 week of stopping therapy, however, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for 1 to 2 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 1 to 2 weeks after the last dose of PONVORY™.

**OVERdosage**

In patients with overdosage of PONVORY™, especially upon initiation/re-initiation of treatment, it is important to observe for signs and symptoms of bradyarrhythmia as well as AV conduction blocks, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed.

There is no specific antidote to ponesimod. Neither dialysis nor plasma exchange would result in meaningful removal of ponesimod from the body. The decrease in heart rate induced by PONVORY™ can be reversed by atropine.

In the event of overdose, PONVORY™ should be discontinued, and general supportive treatment given until clinical toxicity has been diminished or resolved. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

**ADVERSE REACTIONS**

Most common adverse reactions (incidence at least 10%) are upper respiratory tract infection, hepatic transaminase elevation, and hypertension.

Please see Brief Summary of full Prescribing Information on adjacent pages.

INDICATIONS AND USAGE
PONVORY 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.

CONTRAINDICATIONS
PONVORY is contraindicated in patients who:

- In the last 6 months, have experienced 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]
- Have presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, or sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker [see Warnings and Precautions]

WARNINGS AND PRECAUTIONS
Infections
Risk of Infections
PONVORY causes a dose-dependent reduction in peripheral lymphocyte count to 30-40% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2) in Full Prescribing Information]. PONVORY may therefore increase the susceptibility to infections. Life-threatening and rare fatal infections have been reported in association with other sphingosine-1-phosphate (S1P) receptor modulators. In Study 1 of PONVORY phase 3 clinical studies [12.4] in Full Prescribing Information, the overall rate of infections was comparable between the PONVORY-treated patients and those receiving teriflunomide 14 mg (54.2% vs 52.1%, respectively). PONVORY increased the risk of upper respiratory tract infections. Serious or severe infections occurred in 1.6% of PONVORY-treated patients compared to 0.9% of patients receiving teriflunomide 14 mg.

Before initiating treatment with PONVORY, results from a recent (i.e., within 6 months) complete blood count including lymphocyte count should be reviewed.

Initiation of treatment with PONVORY should be delayed in patients with active infection until resolution. Lymphocyte counts returned to the normal active range in 90% of patients within 1 week of stopping therapy in modeling studies. In Study 1 of Full Prescribing Information, 2 patients who received PONVORY at screening and reductions in diffusion lung capacity for carbon monoxide (DLCO) were 61% and 59% in 1 patient at Month 24 and Month 6, respectively. An increase in blood pressure with PONVORY was first detected after approximately 1 month of treatment initiation and persisted.

Herpes Viral Infections
Cases of herpes viral infection have been reported in the development program of PONVORY, herpes simplex encephalitis and varicella zoster meningitis have been reported with other S1P receptor modulators.

In Study 1 of Full Prescribing Information, 4.8% for both PONVORY-treated patients and those receiving teriflunomide 14 mg. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella should be tested for antibodies to varicella before initiating PONVORY [see Vaccinations].

Cryptococcal Infections
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with other 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. PONVORY 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 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, 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 a S1P receptor modulator 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 magnetic resonance imaging (MRI) findings that may be suggestive of PML. MRI findings may appear before clinical signs or symptoms. If PML is suspected, treatment with PONVORY should be suspended until PML has been excluded.

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

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies
Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects [see Drug Interactions].

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

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

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of PONVORY. Avoid the use of live attenuated vaccines during and for 1 to 2 weeks after treatment with PONVORY.

Bradyarrhythmia and Atrioventricular Conduction Delays
Since initiation of PONVORY treatment results in a transient decrease in heart rate and atrioventricular (AV) conduction delays, an up-titration scheme must be used to reach the maintenance dosage of PONVORY (20 mg) [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2) in Full Prescribing Information].

In Study 1 did not include patients who had:

- A resting heart rate (HR) less than 50 beats per minute (bpm) on baseline 12-lead electrocardiogram
- Myocardial infarction or unstable ischemic heart disease in the last 6 months
- Cardiac failure (New York Heart Association class III-IV) or presence of any severe cardiac disease
- Cardiac conduction or rhythm disorders (including sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmia, cardiac arrest) either in history or observed at screening.
- Mobitz Type II second degree AV block or higher-grade AV block observed at screening
- Q-Tc interval greater than 470 ms (females) and greater than 450 ms (males) observed at screening
- History of syncope associated with cardiac disorders
- Uncontrolled systemic arterial hypertension

Reduction in Heart Rate
Initiation of PONVORY may result in a transient decrease in HR. In Study 1, bradycardia at treatment initiation and sinus bradycardia on ECG (defined as HR less than 50 bpm) occurred in 5.8% of PONVORY-treated patients compared to 1.6% of patients receiving teriflunomide 14 mg. After the first titration dose of PONVORY, the decrease in heart rate typically begins within an hour and reaches its nadir within 2-4 hours. The heart rate typically returns to baseline levels 4-6 hours after administration. The mean decrease in heart rate on Day 1 of dosing was 6 bpm. With up-titration after Day 1, the post-dose decrease in heart rate is less pronounced. Bradycardia resolved in all patients in Study 1 without intervention and did not require discontinuation of PONVORY treatment. On Day 1, 3 patients treated with PONVORY had asymptomatic post-dose HR below or equal to 40 bpm; all 3 patients had baseline HRs below 55 bpm.

Atrioventricular Conduction Delays
Initiation of PONVORY treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. In Study 1, the AV conduction delays manifested as first-degree AV block (prolonged PR interval on ECG), which occurred in 3.4% of PONVORY-treated patients and in 1.2% of patients receiving teriflunomide 14 mg. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours after baseline levels 4-6 hours after administration. The mean decrease in heart rate on Day 1 of dosing was 6 bpm. With up-titration after Day 1, the post-dose decrease in heart rate is less pronounced. Bradycardia resolved in all patients in Study 1 without intervention and did not require discontinuation of PONVORY treatment. In Study 1, second- and third-degree AV blocks were not reported in patients treated with PONVORY.

If treatment with PONVORY is considered, advice from a cardiologist should be sought for individuals:

- With significant QT prolongation (QTc greater than 500 msec)
- With atrial flutter/fibrillation or arrhythmia treated with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions]
- With unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), or uncontrolled hypertension
• With a history of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block [see Contraindications]

Treatment Initiation Recommendations

Obtain a complete history and physical to determine whether pre-existing conduction abnormalities are present.

• In all patients, a dose titration is recommended for initiation of PONVORY treatment to help reduce cardiac effects [see Dosage and Administration (2.1, 2.2) in Full Prescribing Information].

• In patients with sinus bradycardia, first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset more than 6 months prior to initiation, first-dose monitoring is recommended [see Dosage and Administration (2.1, 2.2) in Full Prescribing Information].

• PONVORY is not recommended in patients with a history of cardiac arrest, cerebrovascular disease (e.g., TIA, stroke occurring more than 6 months prior to treatment initiation), uncontrolled hypertension, or severe untreated sleep apnea, since significant bradycardia may be poorly tolerated in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

• Use of PONVORY in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

• Experience with PONVORY is limited in patients receiving concurrent therapy with drugs that decrease heart rate (e.g., beta-blockers, non-dihydropyridine calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate such as digoxin). Concomitant use of these drugs during PONVORY initiation may be associated with severe bradycardia and heart block. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

  – For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing PONVORY treatment. If the resting heart rate is greater than 55 bpm under chronic beta-blocker treatment, PONVORY can be introduced. If resting heart rate is less than or equal to 55 bpm, beta-blocker treatment should be interrupted until the baseline heart rate is greater than 55 bpm. Treatment with PONVORY can then be initiated and treatment with a beta-blocker can be reinitiated after PONVORY has been up-titrated to the target maintenance dosage [see Drug Interactions].

  – For patients taking other drugs that decrease heart rate, treatment with PONVORY should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate [see Dosage and Administration (2.3) in Full Prescribing Information and Drug Interactions].

Missed Dose During Treatment Initiation or Maintenance Treatment

If 4 or more consecutive daily doses are missed during treatment initiation or maintenance treatment, reinitiate Day 1 of the dose titration (new starter pack) and follow first-dose monitoring recommendations [see Dosage and Administration (2.4) in Full Prescribing Information].

Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV₁) and reductions in diffusion lung capacity for carbon monoxide (DLCO) were observed in PONVORY-treated patients mostly occurring in the first month after treatment initiation. In Study 1, the reduction from baseline in percent predicted FEV₁ at 2 years was 8.3% in PONVORY-treated patients compared to 4.4% in patients receiving teriflunomide 14 mg. In Study 1, 7 patients discontinued PONVORY because of pulmonary adverse events. There is insufficient information to determine the reversibility of the decrease in FEV₁ or FVC after treatment discontinuation. PONVORY should be used with caution in patients with severe respiratory disease (i.e., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease). Spirometric evaluation of respiratory function should be performed during therapy with PONVORY if clinically indicated.

Liver Injury

Elevations of transaminases may occur in PONVORY-treated patients. Obtain transaminase and bilirubin levels, if not recently available (i.e., within last 6 months) before initiation of PONVORY.

In Study 1, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 4.6% of patients treated with PONVORY compared to 2.5% of patients who received teriflunomide 14 mg. Elevations of ALT to 3-fold the ULN or greater occurred in 17.3% of patients treated with PONVORY and 8.3% of patients treated with teriflunomide 14 mg. The median time to an elevation of ALT was 3 months. The majority (86%) of patients with ALT increases 3-fold or greater the ULN continued treatment with PONVORY with values returning to less than three times the ULN within approximately 2-4 weeks.

In Study 1, the discontinuation rate because of elevations in hepatic enzymes was 2.3% of patients treated with PONVORY and 1.9% of patients who received teriflunomide 14 mg.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, feeling tired, or other gastrointestinal symptoms, should be evaluated with a complete blood count, liver enzymes, and full blood examination (FBE). If elevations of ALT or AST are found, PONVORY should be discontinued and the patient should be reevaluated for any underlying cause.

PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively) [see Use in Specific Populations and Clinical Pharmacology (12.5) in Full Prescribing Information].

Hypertension

In Study 1, PONVORY-treated patients had an average increase of 2.9 mm Hg in systolic blood pressure and 2.8 mm Hg in diastolic blood pressure compared to 2.8 mm Hg and 3.1 mm Hg in patients receiving teriflunomide 14 mg, respectively. An increase in blood pressure with PONVORY was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertensive events were reported as an adverse reaction in 10.1% of PONVORY-treated patients and in 9.0% of patients receiving teriflunomide 14 mg. One patient treated with PONVORY experienced a hypertensive crisis but had evidence of longstanding hypertensive heart disease. Blood pressure should be monitored during treatment with PONVORY and managed appropriately.

Cutaneous Malignancies

Cases of basal cell carcinoma and skin malignancies have been reported in patients treated with S1P receptor modulators, including PONVORY. In Study 1, the incidence of basal cell carcinoma was 0.4% in PONVORY-treated patients compared to 0.2% in patients receiving teriflunomide 14 mg. Comparison to other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with PONVORY and in patients treated with other S1P modulators.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited, and protective clothing and sunblock with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photocchemotherapy is not recommended in patients taking PONVORY.

Fetal Risk

Based on animal studies, PONVORY may cause fetal harm [see Use in Specific Populations]. Because animal reproduction studies are not always predictive of human response, PONVORY should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. PONVORY is not recommended in women of childbearing potential who are not using effective contraception.

Macular Edema

S1P receptor modulators, including PONVORY, have been associated with an increased risk of macular edema. In Study 1, macular edema was reported in 1.1% of PONVORY-treated patients compared to none of the patients receiving teriflunomide 14 mg. A retinal photographic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and again at any time if a patient reports any change in vision while on PONVORY therapy.

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

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

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during therapy with S1P receptor modulators, including PONVORY. Therefore, these patients should have regular follow-up examinations of the fundus, including the macula, during treatment with PONVORY.

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for PONVORY-treated patients in the development program. However, should a PONVORY-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 cerebral ischemia, the physician should promptly scheme 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, PONVORY should be discontinued.
Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation, when initiating PONVORY.

Initiating treatment with PONVORY after treatment with alemtuzumab is not recommended.

Severe Increase in Disability After Stopping PONVORY

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

Immune System Effects After Stopping PONVORY

After stopping PONVORY therapy, ponesimod remains in the blood for up to 1 week. Starting other therapies during this interval will result in concomitant exposure to ponesimod. Lymphocyte counts returned to the normal range in 90% of patients within 1 week of stopping PONVORY therapy in modeling studies [see Clinical Pharmacology (12.2) in Full Prescribing Information]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for 1 to 2 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 1 to 2 weeks after the last dose of PONVORY [see Drug Interactions].

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Infections [see Warnings and Precautions]
- Bradycardia and Atrioventricular Conduction Delays [see Warnings and Precautions]
- Respiratory Effects [see Warnings and Precautions]
- Liver Injury [see Warnings and Precautions]
- Increased Blood Pressure [see Warnings and Precautions]
- Cutaneous Malignancies [see Warnings and Precautions]
- Fetal Risk [see Warnings and Precautions]
- Macular Edema [see Warnings and Precautions]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions]
- Severe Increase in Disability After Stopping PONVORY [see Warnings and Precautions]
- Immune System Effects After Stopping PONVORY [see Warnings and Precautions]

Clinical Trials Experience

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

A total of 1438 MS patients have received PONVORY at doses of at least 2 mg daily. These patients were included in Study 1 (2-year active-controlled versus teriflunomide 14 mg) [see Clinical Studies (14) in Full Prescribing Information] and in a Phase 2 (6-month placebo-controlled) study in patients with MS and the uncontrolled extension studies.

In Study 1, 82% of PONVORY-treated patients completed 2 years of study treatment, compared to 82.2% of patients receiving teriflunomide 14 mg. Adverse events led to discontinuation of treatment in 8.7% of PONVORY-treated patients, compared to 6% of patients receiving teriflunomide 14 mg. The most common adverse reactions (incidence at least 10%) in PONVORY-treated patients in Study 1 were upper respiratory tract infection, hepatic transaminase elevation, and hypertension. Table 1 lists adverse reactions that occurred in at least 2% of PONVORY-treated patients and at a higher rate than in patients receiving teriflunomide 14 mg.

Table 1: Adverse Reactions Reported in Study 1 Occurring in at Least 2% of PONVORY-Treated Patients and at a Higher Rate Than in Patients Receiving Teriflunomide 14 mg

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PONVORY N=565 (%)</th>
<th>Teriflunomide 14 mg N=566 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection ( ^{a} )</td>
<td>37 (6)</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Hepatic transaminase elevation ( ^{a} )</td>
<td>23 (4)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Hypertension ( ^{c} )</td>
<td>10 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\( ^{a} \) Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, respiratory tract infection viral, viral upper respiratory tract infection, tracheitis, and laryngitis.

\( ^{c} \) Includes the following terms: hypertension, hypertensive crisis, blood pressure increased, blood pressure systolic increased, and blood pressure diastolic increased.

In Study 1, the following adverse reactions occurred in less than 2% of PONVORY-treated patients, but at a rate at least 1% higher than in patients receiving teriflunomide 14 mg: viral infection, herpes zoster, hyperkalemia, lymphopenia [see Warnings and Precautions, and macular edema [see Warnings and Precautions].

Adverse reactions in patients treated with PONVORY in an additional 6-month placebo-controlled study were generally similar to those in Study 1. The following additional adverse reactions occurred in at least 2% of PONVORY 20 mg-treated patients and at a higher rate than in patients receiving placebo (but did not meet the reporting rate criteria for inclusion in Study 1): rhinitis, fatigue, chest discomfort, peripheral edema, joint swelling, blood cholesterol increased, migraine, insomnia, depression, dyspepsia, dry mouth, bradycardia, back pain, and sinusitis.

Additionally, in uncontrolled extension trials, the adverse reaction of pneumonia was reported.

Seizures

In Study 1, cases of seizures were reported in 1.4% of PONVORY-treated patients, compared to 0.2% in patients receiving teriflunomide 14 mg. It is not known whether these events were related to the effects of MS, to PONVORY, or to a combination of both.

Respiratory Effects

In Study 1, dose-dependent reductions in forced expiratory volume over 1 second (FEV1) were observed in patients treated with PONVORY [see Warnings and Precautions].

Malignancies

In Study 1, two cases of basal cell carcinoma (0.4%) were reported in PONVORY-treated patients, compared to one case of basal cell carcinoma (0.2%) in patients receiving teriflunomide 14 mg, and a case of malignant melanoma was reported in a PONVORY-treated patient. An increased risk of cutaneous malignancies has been reported in association with other S1P receptor modulators, including PONVORY [see Warnings and Precautions].

DRUG INTERACTIONS

Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

PONVORY 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].

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 effects on the immune system [see Warnings and Precautions].

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

PONVORY can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.
Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs that may Decrease Heart Rate
PONVORY has not been studied in patients taking QT prolonging drugs. Class IA (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 PONVORY is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with PONVORY should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., digoxin) [see Warnings and Precautions and Drug Interactions]. If treatment with PONVORY is considered, advice from a cardiologist should be sought.

Beta-Blockers
Caution should be applied when PONVORY is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of PONVORY [see Warnings and Precautions]. Beta-blocker treatment can be initiated in patients receiving stable doses of PONVORY.

Vaccination
During, and for up to 1 to 2 weeks after discontinuation of, treatment with PONVORY, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during PONVORY treatment and for 1 to 2 weeks after discontinuation of treatment with PONVORY [see Warnings and Precautions].

Strong CYP3A4 and UGT1A1 Inducers
In vitro assessments and limited clinical data indicated that concomitant use of strong CYP3A4 and UGT1A1 inducers (e.g., rifampin, phenytoin, carbamazepine) may decrease the systemic exposure of ponesimod. It is unclear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance. Co-administration of PONVORY with strong CYP3A4 and UGT1A1 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no adequate and well-controlled studies of PONVORY in pregnant women. In animal studies, administration of ponesimod during pregnancy produced adverse effects on development, including embryolethality and fetal malformations, in the absence of maternal toxicity. In rats and rabbits, visceral and skeletal malformations occurred at clinically relevant maternal ponesimod exposures [see Data]. The receptor affected by ponesimod (sphingosine-1-phosphate receptor S1P1) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

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

Data
Animal Data
When ponesimod (0, 1, 10, or 40 mg/kg/day) was orally administered to pregnant rats during the period of organogenesis, increased incidences of postnatal deaths and of low birth weight were observed (syndactyly and ectrodactyly) and cardiovascular system (including ventricular septal defects) were observed at all but the lowest dose tested. A high incidence of embryo-fetal death was observed at the highest dose tested. Maternal toxicity was not observed, indicating a selective effect on the fetus. Plasma exposure (AUC) at the no-effect dose (1 mg/kg/day) for adverse effects on embryo-fetal development in rats was lower than that in humans at the recommended human dose (RHD) of 20 mg/day.

When ponesimod (0, 0.25, 1, or 4 mg/kg/day) was orally administered to pregnant rabbits during the period of organogenesis, an increase in post-implantation loss and fetal variations (visceral and skeletal) were noted at the highest dose tested. No maternal toxicity was observed. Plasma exposure at the no-effect dose (1 mg/kg/day) for adverse effects on embryo-fetal development in rabbits was lower than that in humans at the RHD. In a dose-range finding study in pregnant rabbits, oral administration of ponesimod (0, 6, 20, or 60 mg/kg/day) during organogenesis, an increase in embryo-fetal death and fetal limb malformation (brachydactyly) were observed at the lowest dose tested; at the highest doses, there were no live fetuses. When ponesimod (5, 10, or 20 mg/kg) was orally administered to female rats throughout pregnancy and lactation, the offspring exhibited decreased survival, reduced body weight gain, and reduced fertility and reproductive performance (pre- and post-implantation loss) at the highest dose tested, neurobehavioral impairment (increased locomotor activity) at the mid and high doses, and delayed sexual maturation at all doses tested. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. Plasma exposure (AUC) in dams at the lowest dose tested was less than that in humans at the RHD.

Lactation
Risk Summary
There are no data on the presence of PONVORY in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. When ponesimod was orally administered to female rats during pregnancy and lactation, ponesimod was detected in the plasma of the offspring, suggesting excretion of ponesimod in milk.

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

Females and Males of Reproductive Potential

Contraception

Females
Before initiation of PONVORY treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with PONVORY [see Use in Specific Populations]. Since it takes approximately one week to eliminate ponesimod from the body after stopping treatment, the potential risk to the fetus may persist, and women should use effective contraception during this period [see Warnings and Precautions].

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

Juvenile Animal Toxicity Data
Oral administration of ponesimod (0, 1, 10, 30, or 100 mg/kg/day) to young rats from postnatal day 28 to 91 resulted in lung histopathology (alveolar histiocytosis/edema) and decreased immune function (T-cell dependent antibody response) at the two highest doses tested. Decreased growth (body weight gain and/or long bone length) was observed at all but the low dose, and neurobehavioral impairment (increased locomotor activity) was observed at the highest dose tested. Decreased lymphocyte count and neurobehavioral impairment persisted at the end of a 4-week recovery period.

Geriatric Use
Clinical studies of PONVORY did not include patients 65 years of age and over to determine whether they respond differently from younger subjects.

Use of PONVORY in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Hepatic Impairment
No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) [see Clinical Pharmacology (12.3) in Full Prescribing Information].

PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively), as the risk of adverse reactions may be greater [see Clinical Pharmacology (12.3) in Full Prescribing Information].

OVERDOSAGE

Symptoms and Signs
In patients with overdose of PONVORY, especially upon initiation/reinitiation of treatment, it is important to observe for signs and symptoms of bradycardia as well as AV conduction blocks, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed [see Warnings and Precautions and Clinical Pharmacology (12.2) in Full Prescribing Information].

Active ingredient made in Austria.
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
© 2021 Janssen Pharmaceutical Companies

- computer generated
Questions linger about COVID-19’s origins

Was it natural zoonotic spillover that catapulted SARS-CoV-2 from an emerging virus into a pandemic pathogen, or was it something much more sinister? Could a lab leak in Wuhan, China, have lit the fuse?

Early on, whispers of a potentially engineered virus out of China were so pervasive that, in February 2020, a group of 27 public health scientists published a letter in *The Lancet* disputing the lab leak theory. Analyses of the genomic sequence of the virus subsequently pointed to natural origins, but questions regarding China’s role persisted.

Fast-forward to June 2021, and *The Lancet* has updated the February 2020 letter with an addendum with revised disclosure statements from virologist and investigator Peter Daszak, one of the 27 authors. Daszak noted that his remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York-based nonprofit research foundation of which he is president. The foundation has reportedly worked directly with Wuhan laboratories and funded research at the Wuhan Institute of Virology.

In addition, recent reports have uncovered financial ties between Google and EcoHealth Alliance. The tech giant was accused of censoring lab leak “conspiracy theory” stories in its search results, but Google’s health lead, David Feinberg, M.D., insisted that the company simply took steps to protect users from unverified information.

Are these coincidences or “where there’s smoke, there’s fire” situations? It’s unclear.

The questions extend beyond origin theory, though. With the FDA’s green lighting of vaccines for adolescents and young adults comes hesitation over long-term effects on fertility and cases of heart inflammation. Robert Malone, M.D., the inventor of the messenger RNA (mRNA) vaccine technology, recently expressed concern over the risk-benefit analysis of vaccination for young adults. A CDC advisory committee met recently to discuss cases of myocarditis or pericarditis in people aged 30 and younger who have received an mRNA COVID-19 vaccine.

We may never know where this virus came from and what triggered the global pandemic that has claimed more than 3.8 million lives. And we won’t know the long-term effects until enough time has elapsed. What we do know for certain is that the incredible strength and collaboration of the scientific community have allowed us to regain some semblance of normalcy. The development and rollout of multiple effective vaccine options have been the medical miracle of our lifetime.

That, right now, will have to be the only answer that matters.

Mike Hennessy Sr.
Chairman and founder of MJH Life Sciences

Chairman’s Letter
Mission
Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights and strategies to pursue value-driven solutions.
COVER STORY

CLIMBING THE CAREER LADDER

Profiles of 8 healthcare executives

PAGE 26

DRUGS IN THE PIPELINE
14 2021 starts off strong — and controversial

FORMULARY DEVELOPMENT
16 Generic drug price tags: Too high. And too low. Competition can help create an in-between.

POPULATION HEALTH
24 With income ups and downs, Americans scrimp on healthcare

ONCOLOGY
38 Have we hit the breaking point with oncology drug prices?

42 With accelerated approval pathway, risk of withdrawal looms

INDUSTRY ANALYSIS
46 The advantages of Medicare Advantage

48 Oscar, Bright Health coming on strong

CHRONIC DISEASE
50 Specialists are testing the value-based care waters

TECHNOLOGY
53 The busy signal: Telehealth deals surge as usage stays high

DEPARTMENTS
9 Editorial Advisory Board

12 In Brief

© 2021 MultiMedia Medical LLC All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical including by photocopy, recording, or information storage and retrieval without permission in writing from the publisher. Authorization to photocopy items for internal educational or personal use, or the internal educational or personal use of specific clients, is granted by MJH Life Sciences™ for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400 fax 978-646-8700 or visit http://www.copyright.com online. For uses beyond those listed above, please direct your written request to Permission Dept. email: etemple-morris@mmhgroup.com

Managed Healthcare Executive® does not verify any claims or other information appearing in any of the advertisements contained in the publication and cannot take responsibility for any losses or other damages incurred by readers in reliance of such content.

Managed Healthcare Executive® welcomes unsolicited articles, manuscripts, photographs, illustrations and other materials but cannot be held responsible for their safekeeping or return.

Library Access: libraries offer online access to current and back issues of Managed Healthcare Executive® through the EBSCO host databases. To subscribe, call toll-free 888-527-7008. Outside the U.S. call 218-740-6477.

Managed Healthcare Executive® does not verify any claims or other information appearing in any of the advertisements contained in the publication and cannot take responsibility for any losses or other damages incurred by readers in reliance of such content.

Managed Healthcare Executive® welcomes unsolicited articles, manuscripts, photographs, illustrations and other materials but cannot be held responsible for their safekeeping or return.
IDIOPATHIC HYPERSOMNIA is a rare condition distinct from other sleep disorders\textsuperscript{1-3}

In idiopathic hypersomnia (IH)...

IH is different from other sleep disorders like narcolepsy\textsuperscript{1}

IH is a unique condition with specific AASM ICSD-3 criteria\textsuperscript{4}

ICD-10-CM codes: G47.11, G47.12\textsuperscript{4,6}

There are currently no FDA-approved treatments indicated for IH\textsuperscript{7}

GOOD SLEEP OUTWEIGHS MORE SLEEP

People with IH are getting plenty of sleep, but still feel excessively sleepy during the day\textsuperscript{4,5}

To learn more about IH, contact your Jazz Pharmaceuticals Account Manager or visit SleepCountsHCP.com

AASM=American Academy of Sleep Medicine; FDA=US Food and Drug Administration; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; ICSD-3=International Classification of Sleep Disorders, 3rd ed.


©2021 Jazz Pharmaceuticals plc or its subsidiaries
US-SLE-2100143 Rev0621
In Brief

Prescriptions for what ails value-based care

Everyone seems to be gearing up for value-based care, 2.0. It is hard to argue against the goal of moving from “volume to value.” The jabbing and the jostling are about the best way to get there. Many value-based programs have been launched. The results have been on the “meh” side: mixed and underwhelming. But a new administration in Washington and the appointment of Liz Fowler as director of CMS’ Center for Medicare and Medicaid Innovation (CMMI) are widely seen as an opening to winnow out what hasn’t worked and keep what has.

In February, the University of Pennsylvania’s Leonard Davis Institute of Health Economics took a crack at it in a white paper at sizing up what should happen next with value-based care. Among the suggestions: Simplify the program offerings, accelerate efforts that include downside risk and put an emphasis on health equity.

In June, it was the turn of the experts at the Duke-Margolis Center for Health Policy at Duke University. In a two-part Health Affairs blog post, Mark B. McClellan, M.D., Ph.D., founding director of the center and FDA commissioner and CMS administrator during the George W. Bush administration, and his colleagues outlined “lessons learned” from value-based payment models over the past decade and what they mean for CMS and CMMI. Among their observations was a shortage of specialists in payment reform efforts (see our story on page 50). So far, much of the attention in value-based care models has been on primary care, but the Duke-Margolis team points out that primary care accounts for only 6% to 8% of U.S. healthcare spending.

McClellan and his colleagues also noted that for all its problems, fee-for-service payment has the virtue of being based on a standardized, Medicare-based coding system. The proliferation of value-based care models has led to many different ways of measuring cost, outcomes and quality. “This can be particularly challenging for smaller providers when there are multiple related,” McClellan and his colleagues noted. For similar reasons, they see advantages to multipayer reforms, such as Washington State’s Multipayer Primary Care Transformation Model, a value-based care initiative targeting primary care, and Maryland’s all-payer model, which sets global budgets for hospitals.

Standardize PROs, says FDA draft guidance

In carpentry, it is best to measure twice and cut once. In cancer clinical trials, it is best to measure patient-reported outcomes (PROs) uniformly, according to a new draft guidance from the FDA.

“Heterogeneity of PRO measurement has lessened the regulatory utility of PRO data, says the guidance, which was issued in June. The document recommended sticking to five core PROs: disease-related symptoms, symptomatic adverse events, overall side effect summary measures, physical function and role function. Disease-related symptoms include pain, anorexia and fatigue. Neuropathy is an example of a symptomatic adverse event. The overall adverse event measure can help investigators assess the tolerability of a medication and adjusts for some patients emphasizing certain adverse events more than others, the guidance says. Measuring “role function” is assessing the effect a treatment has on a patient’s ability to work and carry out daily activities.

None of this is uncharted territory, and the guidance points to existing scales and instruments for measuring the core PROs. The guidance also has some suggestions for how often patients should be asked to supply PROs and mentions taking into account the “response burden to patients.” The guidance says baseline assessments should be done to establish a reference point for change and that assessments ought to be done more often during the first few treatment cycles.
In Brief

On June 7, the FDA announced the approval the first new treatment for Alzheimer’s disease in almost 20 years and the first that addresses what many believe is the underlying pathology of the disease.

Controversy ensued.

Three members of the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee, the group of outside experts who had voted against approval of Biogen’s Aduhelm (aducanumab), resigned in protest. The Alzheimer’s Association applauded the approval the day it was announced but a few days later called the estimated annual price (based on the wholesale acquisition cost) of $56,000 as “simply unacceptable.” The Institute for Clinical and Economic Review (ICER) was unstinting in its criticism of the approval and the price. ICER pounced on the day of the approval, issuing a statement that criticized the agency for choosing to “move the goalposts and approve aducanumab based on the surrogate outcome of removing amyloid from the brain rather than the patient-centered outcome of clinical benefit.” Only a drug that halts dementia entirely would merit Biogen’s $56,000-a-year price, said the group’s strongly worded prepared statement. Before the FDA approval, ICER had issued a cost-effectiveness report on Aduhelm that concluded that the most optimistic appraisal of the drug’s efficacy would justify a price of $11,100 to $23,100. As many media reports pointed out, Alzheimer’s disease affects older people, so the cost burden of the drug (and associated imaging studies) will fall mainly on Medicare.

ICER has scheduled a virtual public meeting about Aduhelm and the group’s cost-effectiveness report on the drug for July 15. Anything less than a full house would be a surprise.

Much ado about Aduhelm

On June 7, the FDA announced the approval the first new treatment for Alzheimer’s disease in almost 20 years and the first that addresses what many believe is the underlying pathology of the disease.

Controversy ensued.

Three members of the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee, the group of outside experts who had voted against approval of Biogen’s Aduhelm (aducanumab), resigned in protest. The Alzheimer’s Association applauded the approval the day it was announced but a few days later called the estimated annual price (based on the wholesale acquisition cost) of $56,000 as “simply unacceptable.” The Institute for Clinical and Economic Review (ICER) was unstinting in its criticism of the approval and the price. ICER pounced on the day of the approval, issuing a statement that criticized the agency for choosing to “move the goalposts and approve aducanumab based on the surrogate outcome of removing amyloid from the brain rather than the patient-centered outcome of clinical benefit.” Only a drug that halts dementia entirely would merit Biogen’s $56,000-a-year price, said the group’s strongly worded prepared statement. Before the FDA approval, ICER had issued a cost-effectiveness report on Aduhelm that concluded that the most optimistic appraisal of the drug’s efficacy would justify a price of $11,100 to $23,100. As many media reports pointed out, Alzheimer’s disease affects older people, so the cost burden of the drug (and associated imaging studies) will fall mainly on Medicare.

ICER has scheduled a virtual public meeting about Aduhelm and the group’s cost-effectiveness report on the drug for July 15. Anything less than a full house would be a surprise.

The annual price of Aduhelm, Biogen’s Alzheimer’s drug:

$56,000

Listen to our podcasts!

Managed Healthcare Executive® recently interviewed Ash Shehata, KPMG’s national sector leader for healthcare & life sciences, for its “Tuning In to the C-Suite” podcast. Shehata discussed a recent report by him and his KPMG colleagues titled “From Payor to Healthcare Partner.” The paper highlights how the pandemic drove changes for health plans to adopt a patient-centric model and lists six trends in healthcare to keep an eye on.

“Tuning In to the C-Suite,” is MHE’s home podcast and features healthcare professionals, leaders and executives who talk about the most important, current healthcare issues. Featured on the podcast are podcast subseries “Meet the Board” and “MHE Talks: Improving Patient Access.” You can find episodes of “Tuning In to the C-Suite” and the two subseries on Apple, Spotify and iHeart Radio podcasts or on the MHE website.

Listen in. Learn a lot.
As 2020 came to a close with 53 drug approvals, many wondered about 2021, questioning whether the drugs coming out of the pipeline would slow to a trickle. The answer, so far, is no. As of June 22, the FDA had approved 26 treatments compared with 24 at the same date last year.

The year began with the FDA’s emergency use authorization (EUA) on Feb. 27 for the Johnson & Johnson COVID-19 vaccine, the third such EUA after Pfizer received one for its vaccine on Dec. 11, 2020, and Moderna for its vaccine a week later. But it has been a bumpy road for the J&J vaccine. Its rollout was paused after several cases of a rare disorder involving blood clots were reported. Hopes that the single-shot vaccine would push the vaccination rate up and thereby help the country achieve herd immunity have failed.

Still, as this issue went to press, the pandemic picture was brightening in the U.S. Just over 45% of the population was fully vaccinated, and the seven-day average of new cases of COVID-19 had dropped to just over 10,000, which is 20 times lower than the seven-day average of over 200,000 at the beginning of the year.

Despite concerns that drug approvals might lag because FDA resources would be pulled into reviewing COVID-19 vaccines and treatment, the 26 approvals so far this year tell another story. Among these approvals are some that have been long anticipated and others that have faced their fair share of controversy.

**Alzheimer’s drug controversy**

Easily the most controversial approval was handed to Biogen’s Aduhelm (aducanumab) for Alzheimer’s disease. On June 7, the monoclonal antibody became the first Alzheimer’s treatment approved in nearly two decades and the first that targets the beta-amyloid deposits believed by many to play a causative role in the disease. Aduhelm does not reverse Alzheimer’s but, according to the data on which the approval was based, may slow the rate of cognitive decline.

The approval by itself is significant because millions of Americans with Alzheimer’s may be prescribed the drug. It may also send a fresh signal that beta-amyloid is a good target for Alzheimer’s treatment. Doubts about treating Alzheimer’s by reducing beta-amyloid deposits in the brain had started to creep in as other treatments that focused on beta-amyloid faltered in later-stage clinical trials.

The monoclonal antibody’s fate was unclear until the approval was announced. In 2019, Biogen and Eisai, which co-developed the drug, terminated two late-stage trials for the drug after an independent data monitoring committee determined that the treatment was unlikely to be successful. Based on re-analysis of the data from one of those trials, known as the EMERGE trial, the companies reversed course and applied for approval. At the end of 2020, FDA staffers indicated they backed approval of the drug, but a panel of outside experts, the Peripheral and Central Nervous System Drugs Advisory Committee, effectively voted against approval. Three members of that committee have resigned to protest the FDA approval. Many are questioning the $56,000 price tag, which surpasses expectations and the Institute for Clinical and Economic Review’s cost-effectiveness price range of $11,000 to $23,100 if only the results from the favorable EMERGE trial are used. The FDA used the accelerated approval pathway to approve Aduhelm, which means Biogen will be able to sell the drug for a longer period before other treatments are approved.

2021 starts off strong — and controversial

Not in recent memory has an FDA approval stirred up so much controversy as the agency’s OK of Aduhelm, Biogen’s Alzheimer’s treatment. by JAIME ROSENBERG

Managed Healthcare Executive.com
must conduct a confirmatory clinical trial. Advisory committee members have told journalists that the FDA didn’t tell them about this possibility and that it occurred late in the process. If the positive results from the EMERGE trial don’t hold in the confirmatory trial, then the FDA could pull back its approval.

**KRAS is “druggable” at last**

An increasing number of cancer drugs, particularly those for non-small cell lung cancer, target mutations. But attempts to target mutations to the KRAS gene, which are among the most common, have failed and KRAS was deemed as possibly being “undruggable.” That changed on May 28 with the FDA’s approval of Amgen’s Lumakras (sotorasib).

“The FDA approval of Lumakras is a breakthrough moment for patients with KRAS G12C-mutated non-small cell lung cancer because there is now a targeted therapy for this common, but previously elusive, mutation,” said David M. Reese, M.D., executive vice president of research and development at Amgen, in a press release when the drug received approval.

The approval stems from phase 2 trial data of 124 patients who received the treatment, 36% of whom had at least a 30% decrease in tumor size and 81% of whom responded positively to the treatment. Data presented at the American Society of Clinical Oncology’s annual meeting and reported simultaneously in *The New England Journal of Medicine* show that Lumakras may be especially effective in patients whose tumors have a co-mutation in the STK11 gene. Lumakras, which is taken daily as a pill, is being studied in a phase 3 trial, which will determine how the treatment shapes up against docetaxel.

At the same time, Amgen is testing a lower dose of Lumakras, resulting in some speculation about whether there were safety concerns from the FDA as it reviewed the drug. Amgen also faces questions regarding Lumakras’ $17,900 monthly price tag.

**CAR-T cell therapy**

Another major development during the first half of the year was the FDA’s approval of Bristol Myers Squibb’s and Bluebird bio’s Abecma (idecabtagene vicleucel) for the treatment of multiple myeloma on March 26. Abecma is a chimeric antigen receptor (CAR)-T cell therapy, and prior to this OK, the indications had been limited to acute lymphoblastic leukemia and several different types of lymphoma.

Abecma is approved for patients with relapsed or refractory multiple myeloma who have already received four previous treatments. In a phase 2 trial, the treatment was evaluated in 128 patients who had received at least three prior treatments. After 13.2 months, nearly 3 in 4 patients responded to treatment, and 1 in 3 had a complete response or better.

**Other notable approvals**

Those three treatments and their approvals stand out as the major stories in drug development during a very newsy six months. Here are some other newsworthy approvals:

- **ViV Health’s Cabenuva**, in combination with cabotegravir and rilpivirine, which became the first approved long-acting injectable for the treatment of HIV. Prior to this approval, HIV treatment was limited to pills that need to be taken daily.

- **Merck and Bayer’s Verquvo** (vericiguat) entered a competitive landscape of treatments for heart failure. The chronic heart failure treatment is the first specifically approved for patients who have recently been hospitalized or received diuretics — treatments that promote increased urine production — for acute decompensated heart failure.

- **Sarepta’s Amondys 45** (casimersen), a targeted treatment that gained approval for Duchenne muscular dystrophy, a rare genetic disorder that causes progressive muscle weakness, typically in boys. The injection is designed for patients with the specific type of mutation.

- **Janssen’s Ponvory** (ponesimod) for the treatment of patients with relapsing multiple sclerosis. The treatment, taken as a pill daily, was shown to be more effective than Aubagio (teriflunomide), an established treatment for these patients, in reducing the number of relapses patients experience each year.
Generic drug price tags: Too high. And too low. Competition can help create an in-between.

Low prices and some gaming of regulations can drive out competitors and create monopolies that allow generic makers to jack up their prices. Experience has shown that it often takes multiple generics to achieve the promised-for downward pressure on prices. by DEBORAH ABRAMS KAPLAN

The good news is that generic drug prices are continuing to decrease. As for the rest of the news about generics and biosimilars and their practices, it is complicated. For some classes of drugs, generics remain a price-lowering, cost-saving success. For others, prices are so low that manufacturers may leave the marketplace, creating an opportunity for monopoly pricing. For still others, there is an untapped opportunity for cost savings. "You cannot look at the generic drug and biosimilar markets as homogenous marketplaces," says Martin VanTrieste, president and CEO of Civica Rx, a nonprofit company formed in 2018 to manufacture generic drugs.

For many generics critical to patient care, there are no more savings to squeeze out, says VanTrieste: "If we continue to do that, they will go away." Some manufacturers already produce them at a loss, he adds. But for drugs just coming off patent, "there's a great opportunity to drive the price down to a more affordable level." Generic manufacturers need to file extensive FDA abbreviated new drug applications (ANDAs) and potentially fight off patent lawsuits from brand-name manufacturers first.

Then there are biosimilars, with a more extensive FDA approval process requiring clinical trials, and a more expensive manufacturing process. That lemon is not yet squeezed.

The big picture
Almost 40 years ago, the Hatch-Waxman Act, known formally as the Drug Price Competition and Patent Term Restoration Act, ushered in a new era at the FDA, speeding up approvals and creating a pathway for approving generic medications. Before Hatch-Waxman, less than 20% of prescribed drugs were generic. Generics now comprise 89% of all prescriptions, according to the Association for Accessible Medicines, a trade group for the generics and biosimilars industry. The FDA has approved some 16,000 generic drug applications since passing the Hatch-Waxman Act.

Amendments to the law in 2012 that created a user fee program for generic approvals have also been a major factor in getting more generics on the market.

Generics saved the U.S. healthcare system $293 billion in 2018 alone, according to the FDA, and various other tallies show the savings over the past decade as totaling almost $2 trillion. Although prices have shifted over the years, the Express Scripts overall Price Prescription Index showed generics prices falling 37% between 2014 and 2018, while branded drug prices increased more than 60%. According to 46brooklyn Research, a nonprofit drug pricing research organization, generic drug prices have fallen this year compared with last, notwithstanding some predictions that the pandemic would have the opposite effect. 46brooklyn says driving the overall trend are falling prices for Concerta (methylphenidate), Colcrys (colchicine), Suboxone (buprenorphine-naloxone) and Tamiflu (oseltamivir suspension).

It's all about the competition
Not surprisingly, supply and... Continued on page 22
Based on overall survival (OS) data

The FIRST and ONLY immunotherapy approved in the first-line maintenance setting

BAVENCIO® (avelumab) is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

First-line maintenance treatment of urothelial carcinoma

BAVENCIO® (avelumab) is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

IMPORTANT SAFETY INFORMATION (continues on following pages)

BAVENCIO can cause severe and fatal immune-mediated adverse reactions in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immnosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCIO can cause immune-mediated pneumonitis. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis. BAVENCIO can cause immune-mediated colitis. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone

All randomized patients (major efficacy outcome measure)

- OS was measured post-randomization (after chemotherapy)
- OS in patients with PD-L1-positive tumors (major efficacy outcome measure). BAVENCIO + BSC showed statistically significant improvement in OS vs BSC alone in patients with PD-L1-positive tumors (n=358, 51%); HR: 0.56; (95% CI: 0.40, 0.79; 2-sided P-value <0.001)
- OS in patients with PD-L1-negative tumors (exploratory analysis). In patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18)

Most common adverse reactions in the JAVELIN Bladder 100 Trial

The most common adverse reactions (≥20%) in patients receiving BAVENCIO + BSC vs BSC alone were:

- Fatigue (35% vs 13%)
- Musculoskeletal pain (24% vs 15%)
- Urinary tract infection (20% vs 11%)
- Rash (20% vs 2.3%)

For information on warnings and precautions, see Important Safety Information starting on the previous page.

Study design: The JAVELIN Bladder 100 Trial was a Phase 3, 1:1 randomized, open-label, multicenter study of BAVENCIO as a first-line maintenance treatment in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700)²

BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone
BAVENCIO can cause hepatic toxicity and immune-mediated hepatitis. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation.

Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

BAVENCIO can cause primary or secondary immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withheld BAVENCIO hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hyperthyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 2 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (9/90) of patients with hypothyroidism.

BAVENCIO can cause immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type 1 diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause immune-mediated nephritis with renal dysfunction. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

BAVENCIO can cause immune-mediated dermatologic adverse reactions, including rash or dermatitis. Exfoliative dermatitis including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical steroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

BAVENCIO can result in other immune-mediated adverse reactions. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For neurological toxicities, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

BAVENCIO can cause severe or life-threatening infusion-related reactions. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade 3 reactions were treated with intravenous corticosteroids.

Fetal and other serious complications of allogeneic hematopoietic stem cell transplantation (HSCT) can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

BAVENCIO can cause febrile neutropenia when administered to a pregnant woman. Advise patients of the potential risk to a fetus, including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman not to breastfeed during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

A fatal adverse reaction (sepsis) occurred in one (0.3%) patient with locally advanced or metastatic urothelial carcinoma (UC) receiving BAVENCIO + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonia, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The most common adverse reactions (all grades, ≥20%) in patients with locally advanced or metastatic UC receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 18%), neutrophil open space (24% vs 15%), urinary tract infection (20% vs 11%), and white blood cell decreased (20% vs 10%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ≥20%) in patients with locally advanced or metastatic UC receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (25% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylose increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Please see Brief Summary of Prescribing Information on following pages.

BAVENCIO® (avelumab) injection, for intravenous use

Please see package insert for Full Prescribing Information

Rx only

BAVENCIO® is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-L1 (PD-L1)-PD-L1 binding, the PD-1/PD-L1 pathway. Therefore, removing inhibition of the immune checkpoints can lead to breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may occur even at low doses. While immune-mediated adverse reactions are generally reversible, discontinuation of BAVENCIO during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification of immune-mediated reactions can allow for early discontinuation of therapy. Early diagnosis and treatment of immune-mediated adverse reactions can prevent irreversible damage. Patients should be monitored closely for symptoms and signs of worsening or new-onset symptoms and signs of immune-mediated disease.

Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (26/26) patients with pneumonitis. Pneumonitis occurred in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Nine (0.5%) Grade 3-4 infusion-related reactions occurred with BAVENCIO. Only patients with grade 3-4 infusion-related reactions are discussed below.

Hemolytic anemia, aplastic anemia, and/or thrombocytopenia has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and optionally a corticosteroid may be needed to manage skin toxicity associated with immune-mediated reactions including Grade 3-4 hyperpigmentation, vitiligo, hypertrichosis and hypotrichosis, and alopecia.

Immune-Mediated Nephritis with Renal Dysfunction:

Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification of immune-mediated reactions can allow for early discontinuation of therapy. Early diagnosis and treatment of immune-mediated adverse reactions can prevent irreversible damage. Patients should be monitored closely for symptoms and signs of worsening or new-onset symptoms and signs of immune-mediated disease.

Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (26/26) patients with pneumonitis. Pneumonitis occurred in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Nine (0.5%) Grade 3-4 infusion-related reactions occurred with BAVENCIO. Only patients with grade 3-4 infusion-related reactions are discussed below.

Hemolytic anemia, aplastic anemia, and/or thrombocytopenia has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and optionally a corticosteroid may be needed to manage skin toxicity associated with immune-mediated reactions including Grade 3-4 hyperpigmentation, vitiligo, hypertrichosis and hypotrichosis, and alopecia.

Immune-Mediated Nephritis with Renal Dysfunction:

Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification of immune-mediated reactions can allow for early discontinuation of therapy. Early diagnosis and treatment of immune-mediated adverse reactions can prevent irreversible damage. Patients should be monitored closely for symptoms and signs of worsening or new-onset symptoms and signs of immune-mediated disease.

Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (26/26) patients with pneumonitis. Pneumonitis occurred in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Nine (0.5%) Grade 3-4 infusion-related reactions occurred with BAVENCIO. Only patients with grade 3-4 infusion-related reactions are discussed below.

Hemolytic anemia, aplastic anemia, and/or thrombocytopenia has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and optionally a corticosteroid may be needed to manage skin toxicity associated with immune-mediated reactions including Grade 3-4 hyperpigmentation, vitiligo, hypertrichosis and hypotrichosis, and alopecia.

Immune-Mediated Nephritis with Renal Dysfunction:

Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification of immune-mediated reactions can allow for early discontinuation of therapy. Early diagnosis and treatment of immune-mediated adverse reactions can prevent irreversible damage. Patients should be monitored closely for symptoms and signs of worsening or new-onset symptoms and signs of immune-mediated disease.

Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (26/26) patients with pneumonitis. Pneumonitis occurred in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Nine (0.5%) Grade 3-4 infusion-related reactions occurred with BAVENCIO. Only patients with grade 3-4 infusion-related reactions are discussed below.

Hemolytic anemia, aplastic anemia, and/or thrombocytopenia has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and optionally a corticosteroid may be needed to manage skin toxicity associated with immune-mediated reactions including Grade 3-4 hyperpigmentation, vitiligo, hypertrichosis and hypotrichosis, and alopecia.

Immune-Mediated Nephritis with Renal Dysfunction:
### Table 5: Adverse Reactions (≥10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BAVENCIO plus BSC (N=334)</th>
<th>BSC (N=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td><strong>Grade 3-4</strong></td>
<td><strong>Any Grade</strong></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>32%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16%</td>
<td>2.6%</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>20%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6%</td>
<td>1.1%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>17%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>14%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Cough</td>
<td>14%</td>
<td>4.6%</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypothyroidity</td>
<td>12%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>10%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Fatigue is a composite term that includes fatigue, asthenia, and malaise.
*Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
*Rash is a composite term that includes rash, rash maculopapular, erythema, dermatitis acrodermatitis, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, papular pruritic, drug eruption and lichen planus.
*Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.
*Cough is a composite term that includes cough and productive cough.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO plus BSC.

### Table 6: Selected Laboratory Abnormalities Occurring in ≥10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BAVENCIO plus BSC</th>
<th>BSC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td><strong>Grade 3-4</strong></td>
<td><strong>Any Grade</strong></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>34%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>30%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Blood sodium decreased</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>26%</td>
<td>8%</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) increased</td>
<td>24%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Blood potassium increased</td>
<td>24%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) increased</td>
<td>24%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Blood cholesterol increased</td>
<td>22%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Serum amyloid increased</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>19%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28%</td>
<td>4.4%</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>20%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>18%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*Any test incident is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy, Risk Summary**: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to the fetus. 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.

- **Data, Animal Data**: Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune-related disorders or altering the normal immune response.

- **Lactation, Risk Summary**: There is no information regarding the presence of avemunic in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman to discontinue breast feeding during treatment and for at least one month after the last dose of BAVENCIO due to the potential for severe adverse reactions in breastfed infants.

- **Females and Males of Reproductive Potential, Contraception**: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month before the last dose of BAVENCIO.

- **Pediatric Use**: Safety and effectiveness of BAVENCIO have not been established in pediatric patients.

- **Geriatric Use**: Locally Advanced or Metastatic Urothelial Carcinoma: Of the 344 patients randomized to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were 65 years or older and 24% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

- **PATIENT COUNSELING INFORMATION**: Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Immunemediated Adverse Reactions**: Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
  - Collitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
  - Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.
  - Nephritis: With Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other signs of renal dysfunction.
  - Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of skin rash, itching skin, rash with tiny spots and bumps, reddening of skin, blisters or peeling.

- **Infusion-related Reactions**: Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

- **Complications of Allogeneic HSCT**: Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications.

- **Embryo-Fetal Toxicity**: Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use effective contraception during and for at least one month after the last dose of BAVENCIO.

- **Lactation**: Advise nursing mothers to breastfeed while taking BAVENCIO and for at least one month after the final dose.

Manufactured by: EMD Serono, Inc. Rockland, MA 02370 U.S.A. US License No: 1773 Marketed by: EMD Serono, Inc. and Pfizer Inc. BAVENCIO is a trademark of Merck KGaA, Darmstadt, Germany.

February 2021 US-AVE-00577

Copyright © 2021 EMD Serono, Inc. All rights reserved.
Continued from page 16
demand have an influence on
generic drug pricing. An FDA report
showed that if the generic has no
competition, its average manufac-
turer price — the price that whole-
salers pay to manufacturers — is
39% lower than its brand-name
equivalent. If there are two generic
competitors, the prices are 54% lower
and with four, 79% lower.

There’s a common mispercep-
tion that a brand-name drug’s price
drops when a
generic is coming
on the market, says
Leigh Purvis, direc-
tor of health care
costs and access
at the AARP Public
Policy Institute. In-
stead, the brand usually increases its
price or stays the same. “That makes
it even more important to switch to
the generic, because there’s an even
greater price differential,” she says.

One reason for the brand increase
is that companies sometimes raise
the price of the brand-name drug
in the months before the generic is
available. As a result, the generics
can end up with higher pricing
than that of the brand-name drug,
according to an analysis by GoodRx.

Competition works
both ways
In the generic marketplace, about
one-third of generic drugs lose
money, one-third break even and
one-third make money, according to
VanTrieste. “The ones that are
losing money still make those
products to absorb capacity in their
manufacturing plants to spread
overhead around. It’s better to lose
a little than lose a lot.”

But as soon as they can produce
a money-making product, they’ll
stop manufacturing the
money-losing one. That can cause
drug shortages. Avoiding drug
shortages is one of the reasons
seven health systems and three
philanthropies teamed up to start
Civica in 2018.

“Civica produces on a cost-plus
basis,” VanTrieste says. “Our prices
are completely transparent and
every member in Civica pays exactly
the same price.” The organization
works with other manufacturers to
produce 41 generic medications in
multiple dosage forms, with a goal of
manufacturing 100 drugs by 2023.

Other factors in generic
drug pricing
Drug pricing in general is a black
box, Purvis says, with little to no
transparency in what it costs to
produce drugs and how pricing
is determined. It’s also difficult to
pinpoint why prices increase. Prices
may be driven up because of higher
ingredient pricing or a shortage
of ingredients, or prices are raised
because the product would not be
financially viable to produce other-
wise. These and other factors affect
generic availability and pricing.

Artificial monopolies for older drugs
The FDA’s Drug Efficacy Study
Implementation (DESI) and Unap-
proved Drugs Initiative programs
offer an optional abbreviated FDA
approval process for generics that
entered the market before 1962. In
return for the approved application,
the manufacturer is awarded a mo-
nopoly on marketing the product.
Although initially companies did
not abuse the program, some event-
tually increased prices to resemble
branded pricing, according to Van-
Trieste. Generics competitors can
file an ANDA, but he says it takes
about a year to get the paperwork
together and another year for the
FDA to process it. That gives the
initial manufacturer an artificial
monopoly for at least two years.
Some manufacturers find ways to
extend that monopoly, exclusively
contracting with all active ingre-
dient manufacturers, for example.
Companies making DESI-approved
products sometimes lower the
product price when competitors
are gathering their FDA application
data, so they won’t have a profit
motive. “Knowing that will happen,
other generics don’t enter those
markets,” VanTrieste says. One
example of the jump in pricing is
vasopressin. In the hospital sector,
vasopressin costs rose almost 700%
between 2014 and 2018, after get-
ting DESI approval in 2014.

Orphan drugs
More than 500 drugs without
patent protection have no generic
competition. “Because they (are
for) small populations, there may
not be enough incentives to create
a generic version. They have a mo-
nopoly forever because the generic
manufacturers aren’t attracted to
that product,” Purvis says.

Lawsuits and patent protections
When the patent life runs out,
companies may look for ways
to continue their monopoly. “If
anything, companies are getting
more innovative in finding ways to
extend their monopoly,” Purvis says.
AbbVie obtained more than 100 U.S.
patents for manufacturing process-
es and other issues with Humira;
the initial patent expired in 2016.
The company mounted legal defens-
es against companies that wanted
to launch biosimilars to Humira for
alleged secondary patent infringe-
ment for the drug’s formulation or
delivery. Six biosimilars for Humira
have been approved by the FDA, but
none of them will be on the market until 2023 because of legal settlements with AbbVie.

**Formulation changes**

Some companies change their brand-name drug formulations in attempts to maintain market share. That works for some manufacturers, says David Ridley, Ph.D., a professor and faculty director for health sector management at Duke University’s Fuqua School of Business. But “payers and pharmacy benefit managers have been tougher on the drug markets by declining to put drugs with small tweaks on formulary. The games that drugmakers have tried in the past have been thwarted by some of the managed care practices,” he says.

There are exceptions, including Teva Pharmaceuticals’ Copaxone, a daily injection for patients with multiple sclerosis. Teva changed the 20-milligram daily injection to a 40-milligram dose, injected three times a week. “They were able to hold on to much of the market and hold off competitors,” he says.

**Alleged price collusion**

In June 2020, New Jersey’s attorney general and a multistate coalition sued 26 drug companies, alleging conspiracy to artificially inflate the prices of 80 topical generic drugs. The lawsuit claims a violation of federal and state antitrust and consumer protection laws. This is one of at least three price-fixing lawsuits filed in recent years. “It’s not worth it (to collude) because you’re going to get caught and your company will be embarrassed and have to pay a massive fine,” says Ridley. “When you defraud the federal government, you face potentially enormous penalties. They can threaten to exclude you from doing business with the government, which is a major customer in healthcare.”

**Biosimilar regulations**

Biosimilars are the equivalent of generics for monoclonal antibodies and other large-molecule medications. But the biosimilar market and the dynamics of competition on price have been slow in developing for many reasons, including the “patent thickets” that drugmakers have used to protect their brand-name products and to keep biosimilar competition at bay. Since 2015, 29 biosimilars have been approved for nine reference products and 20 are on the market. “Biologics are living organisms and are substantially more expensive” than other drugs, says Purvis. “A lot of what’s coming on the market are products that won’t face generic competition in the way we’re used to seeing it.” The biosimilar market has been slow to grow, partly because the FDA was slow to give manufacturers guidance, she says. Although costs are generally lower for generic biosimilars compared with the brand, prices are still high. If a drug is $100,000, dropping it by 90% still means a $10,000 bill. “It’s not like where people can get their $5 generic,” Purvis says. The highest discount she’s seen for a biosimilar is 30%. That may change as more biosimilars come on the market and there’s more competition.

FDA approvals for biosimilars require the manufacturer to complete a drug trial. “Although that is costly and painful for the biosimilar manufacturers, it’s good for them in the long run because it helps persuade providers and patients that the products are truly safe and effective,” says Ridley. Longer term, the FDA might relax those requirements, especially if technology allows molecular comparisons to show they’re sufficiently similar. Physicians and other providers currently don’t have much of an incentive to select a cheaper biosimilar when administering drug. Value-based payment models and other payment changes could alter the incentive so use of biosimilars would be to their advantage.

Is there more juice to squeeze from the generic lemon? Yes for biosimilars. Yes to artificial monopolies. Yes to those on extended patent protection. But no to standard generics. “Payers have done an exceptionally good job at driving patients toward generics when available,” Purvis says.

Deborah Abrams Kaplan writes about medical and practice management topics.

**Lack of competition is expensive for Medicare**

The 250 top-selling drugs in Medicare Part D with one manufacturer and no generic or biosimilar competition account for roughly 7% of the approximately 3,500 medications covered by Part D, according to a Kaiser Family Foundation analysis published in April. But the foundation’s analysis found that a relatively small proportion of drugs accounted for more than half (60%) of the net total Part D spending of $145 billion in 2019.
Decades of stagnant wages, a rapidly changing job market, the erosion of employer-based health benefits, and the steadily rising cost of healthcare are leading more Americans to carefully choose which medical treatments they will utilize.

According to results from a recent Brookings study, “Income Volatility and Healthcare Decision-Making,” fluctuating monthly income combined with out-of-pocket costs and high deductibles have become significant factors in the healthcare decisions Americans make. The findings showed that seesawing monthly income and financial navigation through healthcare is a reality for insured people in the middle class, not only for those with low incomes or without insurance.

Recent Kaiser Family Foundation and Los Angeles Times survey findings indicate that 40% of nonelderly adults with employer-based health insurance have difficulty paying their medical bills. Half of those respondents said they or a family member has skipped or postponed healthcare in the past year because of the cost.

“What I hope the audience takes away is just how big a problem (income volatility) is and how widespread financial precarity is throughout the U.S. and that it is creating big problems for many, many people,” said Lisa Servon, Ph.D., the Brookings study co-author and chair of the Department of City and Regional Planning at the University of Pennsylvania Weitzman School of Design, during a recent webinar introducing the study. To understand the effect of income volatility on healthcare decisions, Servon and co-author Mina Addo, a Ph.D. research fellow at the University of Pennsylvania School of Social Policy & Practice, interviewed 33 working adults between the ages of 27 and 55.

The solidly middle-class households (median income between $60,000 and $70,000) had two adults working full time. In half the families surveyed, one of the two working adults also had a part-time job. Ninety percent of the families had health insurance, of which 75% was employment based. The researchers reported that each family, on average, experienced income volatility — that is, five months during the year their income unexpectedly increased or decreased.

On the whole, the families found their copays for primary care affordable. But larger copays or healthcare not covered or partially covered by insurance — dental, vision care, physical therapy, diagnostic testing, serious injury or illness, and chronic issues such as diabetes — presented financial problems.

Some families had health savings accounts to help with bills, whereas others used a credit card. But generally, they simply declined treatment, even for chronic conditions. According to results of a 2018 survey, approximately 60% of Americans said they or someone in their family had a chronic condition and 35% struggle to pay their medical bills.

“I think the eye opener is this is a middle-income, middle-class population,” Addo said of the study’s families during the webinar. “These are a number of people who have done… the right thing. They pursued education, tried to invest in a home. That pathway used to be, I think we would call it, the American Dream.”

Historian James Truslow Adams coined the term “American Dream” in his 1931 book “Epic of America.” Anyone in the United States who had ambition and was willing to work, Adams maintained, could climb their way up the socioeconomic ladder to a “better and richer and fuller life for everyone, with opportunity for each according to ability or achievement.”

If that was ever true, the climb has become steeper and the ladder, more rickety. Since the ‘80s, middle-class wages have risen 6%, whereas upper-class wages have risen 31%. The median house price over that time has climbed 400%. And between
2004 and 2018, out-of-pocket costs for employer-based health insurance rose from $2,600 to $5,000.

Then came the pandemic, the shutdown of in-person activities, and job losses, although some of the overall economic indicators for this year indicate that the economy has rebounded. If there is a winter-gray (not silver) lining to the pandemic, it also has irrefragably revealed that a majority of Americans are living paycheck to paycheck. In fact, almost two-thirds of Americans say they have been living paycheck to paycheck since the beginning of the pandemic, according to results from a November 2020 survey conducted by Highland, a Chicago-based research and design firm.

“With healthcare costs growing faster than wages for several decades, we always knew that the middle class would be squeezed more and more by healthcare as costs grew,” says David T. Grande, M.D., M.P.A., director of policy at Leonard Davis Institute of Health Economics at the University of Pennsylvania. “I think we are getting closer to the point where that squeeze is hitting enough people that costs are a bigger and bigger policy issue.”

**Medicare coverage helpful**

Consumers, Grande says, are frustrated with increasing out-of-pocket costs, limited insurance and narrow networks that can lead to surprise billing from out-of-network providers. Those tactics have probably wrung dry all available savings anyway. So what other solutions do policy makers and insurers have?

The Biden administration is not prioritizing major healthcare reform so far. Even if it were, the chances of a public option or lowering the age of Medicare eligibility would be remote and those for broader Medicare buy-in or Medicare for all, vanishingly small. Medicare expansion of almost any stripe would likely afford some protection against high healthcare costs for the added beneficiaries. “Moving coverage to Medicare means moving some costs to the government and determining how to price that coverage for newly eligible adults,” says Grande. “So the details would really determine what that would mean for consumer costs. But there is a lot of reason to believe that consumers would save money if they gained Medicare coverage.”

There are less ambitious and divisive options pricing transparency rules. Beginning this year, hospitals are required to list the cost for many procedures. Next year the same goes for health insurers, who will have to show how much they pay for services. Will price transparency make a dent in costs?

“It seems obvious that we need more price transparency,” says Grande. “However, by itself I don’t think it will solve our cost issues. A great deal of healthcare spending occurs on services that are not really shopable and well beyond when people have maxed out their deductibles.” The execution of price transparency also leaves a lot to be desired. Hospitals are showing prices, but how transparent (or intelligible) they are is a different matter.

For its part, the Biden administration chipped in by making access to health insurance easier. In March, as part of its American Rescue Plan Act, the administration increased insurance subsidies to people with incomes above 400% of the poverty level who buy health coverage on the ACA exchanges. It also increased the amount of financial assistance for those with lower incomes who were already eligible under the ACA.

Addo would like to see insurers step up and help people find a plan that provides more coverage. “Based on research, some existing plans that are most affordable for consumers (high-deductible plans) do not provide enough coverage to ensure that people can affordably access the care they need,” Addo wrote in an email. Insurers, she says, could improve the situation by helping consumers identify plans that better meet their needs. Grande would like to see the government reach some agreement on a minimum amount of coverage for all Americans, including adjustments to out-of-pocket costs that hinge on income. But is that realistic, given our current health insurance system? “We have to understand that if we choose as a country to continue to rely on a system of private insurance, then insurers will always work to limit spending,” Grande says. “That is the system we have. If consumers want a system that looks more like Medicare, they will have to demand it.”

---

**Robert Calandra** is an independent journalist in the Philadelphia area who covers healthcare.

---

Subscribe to our newsletters for practical tips and valuable resources

Using your smartphone camera, hover over the QR code.
When Managed Healthcare Executive® interviewed eight healthcare executives about their careers, we learned that their ascents were not always steady climbs. They had twists and turns, jumps ahead and slips back. Outside events and larger trends shaped career ladders in unexpected ways, adding and subtracting rungs and bending side rails. Even so the most powerful force for many has been their own sense of purpose, a North Star of some kind. And colleagues, co-workers and teams have boosted, supported and sustained.
From amazement to aiming to be more like Amazon

When Romilla Batra, M.D., MBA, came to the United States from her native India to continue her medical training, she was “beyond amazed,” she recalls.

After working in an emergency room treating pediatric patients in inner-city Delhi, where “simple stuff could make a big difference; dehydration could kill,” Batra came to the University of California, Los Angeles (UCLA), at age 26, to train in internal medicine. There she had access to equipment and technology that are taken for granted in the United States, such as MRIs. In India, “an MRI was like doing a transplant. It was really so rare.” In India she relied on her “hands, ears and eyes” and would assume the role of doctor, surgeon and nurse, all in the span of a single night. At UCLA, Batra says, she learned about treating patients with complex medical needs: “In a way I felt like I knew a lot. In a way I felt like I knew nothing.”

After UCLA, Batra headed to Indiana University School of Medicine, where she served as medical director, and then returned to California to become medical director at University of California, Irvine (UCI). Along the way she got her MBA and she continues to teach at UCI’s medical and business schools.

Batra also learned to work with a broad range of patients with diverse backgrounds, cultures and languages, such as African Americans, Hispanics and Vietnamese. “The dynamics are very different,” says Batra. Batra began to focus on population-based approaches to healthcare and how to scale programs to make them more effective for a wider range of patients.

In 2011 Batra, who is board certified in internal medicine, became vice president and medical director at SCAN Health Plan, a not-for-profit Medicare Advantage plan in Southern California, and held several positions before becoming chief medical officer.

When she joined SCAN, her patients were sad to see her leave full-time clinical practice. Some gently joked that “I went to the dark side of the world,” Batra says. But she was drawn to the payer because “its mission resonated so strongly with me,” she says.

With the move she could take a population health approach to reach SCAN, which now has 220,000 members in 11 counties in California.

She says she works to teach medical and business students “how to think outside the box to improve the experience of the people we serve and how do we do it in a sustained manner.”

American healthcare, she believes, needs to emulate retailers such as Costco and Amazon, which deliver effective, efficient service.

In healthcare, “service is downgraded,” Batra says. Payers and providers need to learn to think about “what does the consumer want” and consider “how do we engage with them, so they are more likely to follow what we want them to follow” when it comes to improving their health. “The focus should be on “how do we change their behavior, change their lifestyle,” she says.

At SCAN, Batra says she is “surrounded by an amazing group of people. When you have passion and passion is your job, it just becomes so much fun.”

—Susan Ladika
Climbing the career ladder

Understanding gained at the entry level pays off

Koleen Cavanaugh grew up in Maryland but went to college at Villanova University, outside of Philadelphia. She fell for the city. “I knew I wanted to stay here after I graduated, but the job market was not great at the time,” she says. Armed with a bachelor’s degree in communications with a minor in English, in 1991 she took a position in customer services at Independence Blue Cross (IBX), a Blues plan with an 80-year history in Philadelphia. “I wouldn’t say I had a dream of necessarily being in healthcare. But what I really wanted to do is help people through communications and work with people to help them better understand products, services, etc.” Cavanaugh explains. “Starting in customer service was the best thing for my career as it allowed me to completely understand the ins and outs of all of the products that we offer.” That firsthand experience was instrumental as Cavanaugh rose through the ranks of the company. Thirty years later, she is vice president of marketing at IBX. “When I started in marketing, I really understood what people understand and didn’t understand about the products and where we needed to be clearer in the way that we communicated certain benefits and services,” Cavanaugh says. “Others may have had a marketing background or had more experience from a marketing perspective, but they didn’t understand how the products really worked like I did.”

She learned negotiation skills, how to work closely with a sales team and how to deal with external vendors. “Understanding how to manage a vendor relationship was extremely pivotal as my career grew and important for me to ultimately negotiate contracts,” Cavanaugh says. “That groundwork helped when I was promoted to manage the department.” In her current role, Cavanaugh leads different marketing teams, including a client broker team focused on the life cycle of customers who purchase coverage for their employees. There are also teams that focus on the member side of things and corporate marketing. “We also have a very robust engine driving digital engagement with our members, and two-thirds of our subscribers have opted in to receiving digital messaging from us,” Cavanaugh says.

Cavanaugh says one of things she’s proudest of her in her career is the approach that IBX took to the ACA. “We as an organization decided we were going to fully embrace the ACA and saw it as a huge opportunity for us to really live up to our social mission,” she says. IBX set up mobile education and enrollment centers. “We were out in festivals and fairs and block parties, so we created awareness anywhere we could,” Cavanaugh says. The insurer also used a variety of direct mail and social media strategies. It paid off. During the first enrollment period, 90% of consumers who purchased a product on the ACA exchange for southeastern Pennsylvania bought an IBX product.

There’s still a lot that Cavanaugh hopes to accomplish with the company. A big part of her focus this year has been on equity in healthcare and in the delivery of healthcare. She also is examining how IBX can leverage what it does as a health insurer to ensure that it’s bringing health equity to all its members and the communities it serves. “We’re really focusing on the whole-person health, not just the medical side, but also the mental health and behavioral health side of things,” she says. “We’re looking at how we can continue to improve access for members and on education.” Having been at IBX for her entire career, Cavanaugh obviously knows what it takes to be successful. “My advice for people coming up in this business is just to always stay positive,” Cavanaugh says. “No matter what level of an organization that you reach, I think it’s always important to stay inquisitive to understand how things work and the impact that you’re having on your customers.”

—Keith Loria
Angela Celestin proves you don’t have to come up through the healthcare industry to be successful in the field. The skills learned in other industries can be transferable for those ready to make the switch to healthcare.

Celestin, who is now executive vice president and chief human resources officer for CareFirst BlueCross BlueShield, based in Baltimore and Washington, D.C., had HR roles in the food and beverage, publishing and financial services industries before making the jump to the health insurer two years ago.

Moving from industry to industry, Celestin has seen that “people are people. Employees are employees.”

The New York native grew up in public housing in Brooklyn and went to Cornell University, where she planned to be a lawyer. But PepsiCo recruited her for a minority internship program during her sophomore year of college. “That began my career in HR,” says Celestin.

She graduated with a degree in industrial and labor relations and joined PepsiCo full time. The food and beverage giant “gave young people a lot of responsibility at a very early age,” says Celestin, who was involved in contract negotiations and ran training courses on topics such as sexual harassment and workforce discrimination. PepsiCo embraced the need for employee diversity and even in the early 1990s, the company “had diverse hiring goals way before that was a thing,” Celestin says. Her career with PepsiCo took her to small towns in the Midwest, and that continued when she took an HR job with the printing company, R.R. Donnelley & Sons. Those experiences outside the big city “really grew me as a person,” she says. One of her responsibilities at R.R. Donnelley was leading diversity training courses for the company, which had few minority employees at the time.

Her next move was into financial services, working in HR executive roles for Citibank in Chicago and New York. She then moved to OneMain Financial and Money Mart Financial Services, where she served as executive vice president and chief human resources officer.

Celestin says she was attracted to CareFirst because she knew “healthcare was going through some major changes, and I wanted to be part of that change.” From her work in the financial services industry, she often dealt with customers “in their time of need. I saw a correlation” between finance and healthcare, she says. Celestin also sees similarities in dealing with consumers in healthcare and at companies such as Money Mart, where disparities exist. “Healthcare is still inequitable for many Americans. The type of healthcare you receive depends on where you grew up, your neighborhood, your race.”

One big difference between financial services and healthcare was that “the lack of embrace of technology (in healthcare) was surprising to me. Technology has changed banking so much,” Celestin says.

With technology in banking “the focus is on the customer. The focus is on the ease of the transaction.” Healthcare, on the other hand, has been slow to “meet customers where they are,” Celestin says.

But she sees that changing because of the COVID-19 pandemic, as healthcare organizations and consumers made an abrupt shift to virtual care. As the pandemic has fueled the adoption of telehealth, Celestin hopes it will help “make healthcare accessible to all.”

—Susan Ladika

Continued on page 33
TRODELVY attacks tumors with an antibody-drug conjugate (ADC) that binds to Trop-2.1

Based on preclinical data. May not correlate with clinical outcomes.

INDICATIONS
TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:
- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: NEUTROPENIA AND DIARRHEA
- Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm3 or neutrophilic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
- Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

CONTRAINDICATIONS
- Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS
Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm3 on Day 1 of any cycle or neutrophil count below 1000/mm3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can be treated with atropine.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.
INDICATIONS

OFFER A DIFFERENT POSSIBILITY.

SCAN TO VISIT TRODELVYHCP.COM.

Based on preclinical data. May not correlate with clinical outcomes.

TRODELVY attacks tumors with an antibody-drug conjugate (ADC) that binds to Trop-2. 1

TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease.

CONTRAINDICATIONS

Severe, life-threatening, or fatal neutropenia can occur and may be contingent upon verification and description of clinical benefit in confirmatory trials.

ADVERSE REACTIONS

In the ASCENT study (IMMU-132-05), the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (≥1%) were neutropenia (7%), diареhеа (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

In the TROPHY study (IMMU-132-06), the most common adverse reactions (incidence ≥25%) were diarrhea, fatigue, neutropenia, nausea, any infection, alopecia, anemia, decreased appetite, constipation, vomiting, abdominal pain, and rash. The most frequent serious adverse reactions (SAR) (≥5%) were infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), and sepsis or bacteremia (5%). SAR were reported in 44% of patients, and 10% discontinued due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the TROPHY study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.


Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.
Grade 4 infusion-related reactions. Anaphylactic reactions was 0.3%. Premedication for infusion reactions in patients receiving TRODELVY is recommended. The median time to Grade 1–3 infusion-related reactions following the initial 1-h infusion and for at least 30 minutes after infusion.

Dose Reductions for Infusion-related Reactions: Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for the threatening infusion-related reaction.

Severe Neutropenia: Grade 4 neutropenia occurred in 7% of patients. Grade 3–4 neutropenia occurred in 2% of patients. Treatment delays or dose reductions were required due to neutropenia. Neutropenic fever occurred in 13% of patients. Grade 3–4 neutropenia occurred in 7% of patients. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Thrombocytopenia: Grade 3–4 thrombocytopenia occurred in 2% of patients. Grade 3–4 neutropenia and anemia was analyzed in 701 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 4 neutropenia was 66% in patients homozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=393). The incidence of Grade 4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 19% in patients homozygous for the wild-type allele, 18% in patients treated with TRODELVY and 5% in patients treated with single-agent chemotherapy. Consider TRODELVY in patients with evidence of adverse early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 activity for adverse reactions. Withholding or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of adverse early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 activity for adverse reactions.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SR-38, and targets rapidly dividing cells. Advise pregnant women of the potential for reproductive toxicity and advise women to use effective contraception during treatment with TRODELVY and for 6 months after the last dose of TRODELVY. Advise male patients with female partners of the potential for reproductive toxicity and advise women to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

See also BOXED WARNING, Warnings and Precautions, and Clinical Studies. The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in 759 patients from three studies, MMW-132-01, MMW-132-05 and MMW-132-06 which included 366 patients with mUC who had previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the unique dihydropyridine glucosyltransferase 1A1 (UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, bone marrow/organ-threatening toxicity, and anemia and may be at increased risk for developing Grade 4 neutropenia and anemia in 701 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 4 neutropenia was 66% in patients homozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=393). The incidence of Grade 4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 19% in patients homozygous for the wild-type allele, 18% in patients treated with TRODELVY and 5% in patients treated with single-agent chemotherapy. Consider TRODELVY in patients with evidence of adverse early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 activity for adverse reactions. Withholding or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of adverse early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 activity for adverse reactions.
Eric Hunter might have had a career in the oil patch rather than in healthcare were it not for a winning gubernatorial campaign.

Hunter majored in petroleum engineering at University of Tulsa in Oklahoma, but the struggling oil industry of the early 1990s led him to reexamine his career path. In 1990, Hunter joined the Oklahoma gubernatorial campaign of David Walters. After Walters, a Democrat, won, he hired Hunter to be the executive director of boards and commission for the governor’s office. Hunter became involved in the launching of Oklahoma’s Medicaid managed care, and he eventually moved to the newly created Oklahoma Health Care Authority, which administers the Medicaid program.

He says his work habits came from his parents, who worked hard to be the first generation of their families to go to college. And although Hunter initially had his sights set on majoring in engineering, they also gave him footsteps to follow into healthcare. His father, Charles, was a U.S. Army medic and lab technician. His mother, Theresa, was a nurse.

The ACA added another fortunate turn to Hunter’s career. He was working for ValueOptions Behavioral Health in Dallas as the provisions of the landmark healthcare reform law were being implemented. ValueOptions had a North Texas Behavioral Health Authority contract for behavioral health and substance use disorder services. "As valuable as I knew the behavioral health system was to community health, I recognized that I wanted to be involved in work that encompassed more of the individual and community healthcare continuum."

So Hunter pulled up stakes and headed to Boston, where he was chief operating officer at the Boston Medical Center HealthNet Plan, a Medicaid managed care organization, from 2013 to 2016. While working in Boston, he earned his MBA from Northeastern University. He has been president and CEO of CareOregon, a 500,000-member Medicaid managed care plan in Portland, since June 2016.

Hunter says he likes to believe that he was hired as CareOregon’s CEO because of his willingness to manage work in multiple states and different types of health plans over the years. "Building relationships with people through professional organizations and prior assignments kept me on the radar for the right opportunities," Hunter says. "Being willing to participate in and learn from leaders at ACHP (Alliance of Community Health Plans), ACAP (Association for Community Affiliated Plans) and IHI (Institute for Healthcare Improvement) not only educated me in the business but also helped to build those relationships."

With CareOregon, Hunter continues, he has the honor of managing an established entity with strong community ties and a presence based on innovation, partnership and cooperation. "We have no ownership or governance barriers to doing the right thing for our members and the safety net providers who serve them."

Reflecting on his own career ladder, Hunter says that being bold and believing in yourself are key to career success. It may be scary, but he says growth takes place when people get out of their comfort zone.

"You must be open to incorporating new ideas into your thinking to take the best of all your experience forward," Hunter advises. "Changing companies or volunteering for new assignments in your current company may give you trepidation, but by expanding your base of knowledge, you will be more open to new ideas and more inclined to use best practices wherever you go."

—Briana Contreras
Climbing the career ladder

Threats of violence and virulent anti-Semitism were the future for then-11-year-old Ramin Davidoff had his family stayed in the city of Urmia in northwest Iran as the nation’s revolution unfolded in 1979.

His parents, however, decided to flee for a month or two until the revolution subsided, and headed for northern Utah, where his uncle was attending Utah State University. The revolution dictated that the short stay would become permanent.

With the chance to fully use his talents, Davidoff would soon be on a steep ascent that in January 2021 landed him as co-CEO of the Permanente Federation, a consortium of all the Permanente Medical Groups in the nation, supporting nearly 23,000 Permanente physicians.

“We were very fortunate to move to the United States, which really has become for me a land of opportunity, although at 11 I did not realize that,” Davidoff says.

Davidoff’s career path has been on an upward trajectory. He went to University of California, Irvine, for eight years, first as an undergraduate and then as a medical student, completed his residency training in urology at Kaiser Permanente Los Angeles Medical Center and chose to remain in the system.

“Medicine for me truly was, right from the beginning, about what’s best for the patient,” Davidoff says. “When that happens in training, then it stays with you, and I truly appreciated that brand of medicine.”

Davidoff never envisioned going into administration. His opportunity came at Baldwin Park Medical Center when he took on the role of physician director of risk management and patient safety. He saw it as a way to improve patient care more broadly by focusing on safety. Tearing down the pyramid structure that saw the physician at the top was part of his strategy. “I wanted it flattened, a system where every member of the team had an opportunity to have a say in the care,” Davidoff says.

Davidoff would rise to become assistant medical director. When he was elected to the Southern California Permanente Medical Group board of directors, which he now chairs, he suddenly had an additional perspective on care, this time from the governance angle.

“That was also a very important lens,” he says. “That’s where the strategy, the business, the finance, the competitive landscape — all the things that are important to run a higher-performing medical group — came into play.”

Davidoff was fortunate to be given nine months to transition into his role as co-CEO of the Permanente Federation. Unfortunately, it coincided with the pandemic.

“I’ve always focused on our people, but even more so in the early part of the pandemic,” he says. “These people have fear. They’re worried about coming into work, eventually getting infected and taking the infection back to their families. So there was a real importance of communication and being real and genuine with them, really being visible.”

The lesson of the pandemic, he said, was innovation. The system has pivoted toward telehealth and virtual work. Many patients who normally would have been hospitalized, it turned out, could be managed safely at home with monitoring systems.

“Through it all, Davidoff says, the values he learned as a boy are the same ones he urges those in the medical field to follow today. “There’s no substitute for working hard and to always treat your people kindly, professionally and respectfully,” he says. ”That will allow them to be who they are in work environments and brings out the best in them.”

—Larry Hanover
Climbing the career ladder

Deadly hospital error leads to a commitment to quality

Jennifer Sheets might have had a career in insurance instead of healthcare. Her family owned an independent insurance agency, TP Frye and Associates in Bristol, Virginia, a small town in southwest Virginia that straddles the Virginia-Tennessee border. The agency, which is now called Frye-Shaffer Insurance, and is owned by her brother, sold all types of insurance: auto, home, business, boat, health and life. When she was 10, Sheets was a part of the “licking and sticking” crew, as her parents called it, that was responsible for readying the bulk mailings after school each day. By the time she was old enough to drive, she was inspecting and taking pictures of insured properties. As a college student, she became a licensed insurance agent, processing new applications and quoting renewal rates.

But Sheets wanted a career in healthcare. She studied nursing at the University of Virginia’s College at Wise. After graduating, she went to work where she believed she could make a big difference in people’s lives: the trauma and transplant intensive care units at Johnson City Medical Center in Tennessee, and then she moved to the Grand Strand Medical Center in Myrtle Beach, South Carolina.

“Starting my career as an RN made me aware of the dedication and heart it takes to serve others,” Sheets says. “Although I no longer work at the bedside, I maintain my license today and use many of the skills I learned on the job: empathy, problem solving and communication.”

Sheets scrambled up the career ladder in a hurry. She held various leadership positions, first as a director at Regency Hospital Company, which focuses on rehabilitation for patients, and then assumed clinical leadership roles at several providers, including Kindred Healthcare in Louisville, Kentucky, where she became CEO in 2008 when she was just 35. Sheets says her career and focus on quality and care at home was shaped by her father’s death from a preventable clinical error.

“My father went from being a company founder, president and CEO who ran five miles a day to being in a comatose state within minutes because of an easily prevented hospital error,” Sheets says. “He underwent a very routine outpatient procedure (but) post-procedure orders and protocol were not followed. He went into respiratory arrest and sustained a severe anoxic brain injury that took his life. My commitment and passion for high-quality, process-driven healthcare (are) still greatly fueled by the horrific event that absolutely didn’t need to happen.”

From that point on, she says, she was committed to working to ensure that people can age in place and stay in their homes as long as possible: “I moved into the home health and hospice space because I know that this is where people want to be, where the outcomes are better, and it’s how we can keep people from needing to go to the hospital in many situations,” she says.

Sheets has been president and CEO of Interim HealthCare, a home health-care and hospice provider and staffing company in Sunrise, Florida, and its parent company, Caring Brands International, for two and a half years.

Sheets has been president and CEO of Interim HealthCare, a home health-care and hospice provider and staffing company in Sunrise, Florida, and its parent company, Caring Brands International, for two and a half years.

She says she sees herself as a “lifelong nurse who just happens to be in a CEO role right now.” When reflecting on her life and career experiences, Sheets advises anyone, regardless of their career path, to make sure they’re staying hungry for knowledge and looking for where they can provide the greatest impact. “Do something you love and are passionate about,” she says. “That’s the key to being successful and continuing to move up the ladder.” And Sheets says anybody taking care of patients needs to see every patient as somebody’s family member. And to keep caring: “If you ever get to the point where a bad outcome doesn’t bother you, quit. You’re not in the right profession.”

—Briana Contreras
See challenges? Head in that direction

Rahul Sharma, M.S., CEO of HSBlox, learned early in his career to take risks, build a team that works well together and focus on solving the harder problems that bring value to the industry and the shareholders.

“I also learned to be the bridge between business teams and technical teams to help provide solutions that bring the vision to life and bring value to everyone in the ecosystem,” he says.

Born and raised in northern India, Sharma spent the first 23 years of his life in India and the past 25 in the United States. As a youngster he played cricket and soccer, both competitive team sports, which helped instill in him discipline.

Sharma earned his bachelor’s degree in engineering from the Indian Institute of Technology Roorkee in 1995 and then his master’s degree, also in engineering, from the University of Alabama in 1998.

He worked in India for the Tata Group before coming to the U.S. His first jobs in this country were with Peachtree Software, an accounting software firm that pioneered online accounting, and Manhattan Associates, a supply chain software company. At Manhattan Associates, he led the systems and database services group in the research and development department. The clients included Walmart, Mary Kay, Dell, Home Depot and the Mayo Clinic. After a seven-year stint, Sharma “took the entrepreneurial route,” a path that has included spearheading five startups.

Sharma’s introduction into healthcare came when he built a SaaS-based solution called VIMS (Vaccine Inventory Management System) at his first company, Decipher Information Systems. But then he shifted gears and partnered with Davidi Gilo, an Israeli entrepreneur, to build INVeShare, a fintech company. Sharma’s other startups included Bloxshare, which offered a blockchain platform for the fintech industry; PatientBlox, which built a prospective bundled payments platform that enabled payer and provider collaboration; and now HSBlox, a healthcare technology company whose CureAlign platform connects community care networks to address social determinants of health issues.

Sharma says he has a passion for building out great teams and tackling difficult problems. “This creates opportunities for our team members and value for our shareholders and the industry,” he says. “We have shown with our sister company PatientBlox, which we sold to Signify Health last year, that difficult problems like prospective bundled payments can be addressed with proper thought leadership and a technical solution that addresses those points.”

The current model of American healthcare is focused on “sick care” and crisis management, says Sharma. Perhaps it is his training as engineer; Sharma thinks that can be fixed with the right application of technology and data.

“One of the key reasons for this (the focus on sick care) is the data challenge that exists in the industry, not only pertaining to interoperability, but also to digitization of the wealth of data that is available in unstructured and semistructured data sets,” Sharma says. “In order to move towards value-based care programs, we have to start addressing the social determinants of health more adequately.”

Sharma says some challenges of traveling upstream to the social determinants of health can be overcome with digitization of the data, forming a longitudinal healthcare record — an LHR to go along with the electronic health record (EHR). The LHR could be used for better predictive and risk-score analysis.

“Technology exists today that can help us achieve these objectives and help us to be more proactive in providing care, and, hence, intervene before issues become a crisis,” he says.

—Keith Loria
Hitting the right notes

His passion was for music, specifically for the French horn, the curlicue brass instrument that is notoriously difficult to play. Being a pharmacist was strictly for paying the bills. While pursuing a master’s at Carnegie Mellon University in Pittsburgh, Michael Zeglinski squeezed in two days a week as a pharmacist. His master’s thesis was on the French horn parts in Gustav Mahler’s symphonies, and he studied with the principal horn player for the Pittsburgh Symphony Orchestra. There was an audition for the orchestra and gigs playing in the orchestra for the Pittsburgh Opera.

“But if you’re going to be a symphony-level musician and have that as your career, you need to have that je ne sais quoi, or that talent, that pushes you over the edge,” says Zeglinski. “I was kissing the pinnacle but never quite felt I was going to be able to stay there for 20 to 30 years.”

Zeglinski has reached a different sort of pinnacle — and stayed there — as a pharmacist and healthcare executive. The senior vice president and CEO of specialty and infusion pharmacy at OptumRx oversees a part of the business that accounts for roughly 10% of UnitedHealth Group’s revenues, and Zeglinski sits atop an organizational chart with roughly 6,000 employees.

Zeglinski’s first full step into the executive career track was with Gentiva Health Services, a specialty pharmacy in Warrendale, Pennsylvania, outside of Pittsburgh. As with many people in healthcare, Zeglinski’s career path has been rerouted, then rerouted again, by acquisitions in a Russian nesting doll pattern. Gentiva’s pharmacy business was sold to Accredo, which was bought by Medco, which now part of Express Scripts, which was acquired by Cigna. He is at OptumRx because the company that hired him became Catamaran, which was acquired by Optum. In between, he had a stint of about 10 years with CVS Caremark, CVS Health’s PBM.

At Optum, Zeglinski’s career has gone back to his roots. “I worked in specialty pharmacy before it was even a word,” he says. “So as specialty developed, I moved out of infusion into specialty, and now I am back to where I am managing infusion, although there’s now an overlap. Before they were bifurcated.”

Zeglinski wants to bring more self-service and digital tools to specialty and infusion pharmacy. “In specialty pharmacy we always said, ‘Oh we are high-touch specialty pharmacy, etc.,’ which means I know more than you, the patient. I’m here as the doctor, the pharmacist, and I’m going to tell you what you need to do,” he says. Self-service and digital services can help patients take care of themselves. “Why do they have to talk to me every month to get their prescription?” he asks. “If I were a patient, I would only want to get on the phone and talk to us when I wanted to, not the other way around. So how do we get there?” says Zeglinski.

—Peter Wehrwein

Michael Zeglinski
OptumRx

Managed Healthcare Executive.com
Have we hit the breaking point with oncology drug prices?

Some see the upward trend in cancer drug costs as accelerating — and unsustainable. Value-based pathways might rearrange the incentives to put some downward pressure on prices. by PETER WEHRWEIN

Cancer care is expensive and there have been countless journal articles, presentations and reports about why and what might be done about it. But now the worry has hit a new phase. Providers, payers and patients are wondering whether the cost, especially the cost of cancer medications, is sustainable.

In JAMA Oncology, three prominent oncologists compared the trend in cancer drug costs to the famous “hockey stick” graph showing the sudden rise in global temperatures in the late 20th century. Blase N. Polite, M.D., M.P.P., and Mark J. Ratain, M.D., oncologists at the University of Chicago, and Allen S. Lichter, M.D., former CEO of the American Society of Clinical Oncology, wrote that data from CMS’ Oncology Care Model show that drug costs accounted for more than 50% of the total cost of oncology care in 2018 and that proportion is projected to increase this decade. “What might the practice of oncology look like if the costs of the drugs alone exceed 80% of the cost of taking care of patients during the active phase of their care?” they asked rhetorically.

Chimeric antigen receptor (CAR)-T cell therapies, which involve genetically engineering a patient’s T cells so they recognize cancer cells, are among the most expensive cancer therapies. Prime Therapeutics, a PBM owned by 19 Blues Plans, presented a study at the Academy of Managed Care Pharmacy meeting in April that showed the cost is not just limited to the treatment period. Prime’s researchers identified 74 members over a 2.5-year period who received CAR-T cell therapy for B-cell lymphoma. Their real-world data study showed that almost 40% of those members did not have a durable response to CAR-T cell therapy. Prime’s cost figures show that CAR-T cell therapy alone cost $527,000 during the initial treatment period and that 12% of those with events after the initial period had care that resulted in healthcare costs of more than $1 million.

Costs as high as those invite cost-effectiveness scrutiny. The Institute of Clinical and Economic Review (ICER), the value assessment nonprofit group in Boston, issued its final report on the cost-effectiveness of two CAR-T cell therapies for multiple myeloma, Abecma (idecabtagene vicleucel) and ciltacabtagene autoleucel, in May. A third medication, Blenrep (belantamab mafodotin-blmf), an antibody-drug conjugate, was also analyzed. To meet the standard cost-effectiveness of threshold of $100,000 per quality-adjusted life year (QALY), the ICER report says Abecma’s current annual price of $419,500 would need to be slashed by 37%-54% and ciltacabtagene autoleucel, which isn’t on the market yet, would need to be priced at about $300,000. Blenrep’s current price falls within acceptable cost-effectiveness thresholds, according to ICER.

Polite, Ratain and Lichter map out possible responses to rising cancer drug prices: shifting costs to patients (which would likely price many patients out of the care they need) or shifting financial risk on to providers via bundled payments and the like (which many providers will resist if the financial risk is too great). They portray “value-based pathways” as a hopeful alternative. Deviations from the pathways would result in financial penalties and adherence, in bonuses. If oncologists had a strong enough incentive to avoid prescribing low-value treatments, pressure to lower drug prices would follow, in their estimation, and drugmakers would start to develop drugs with value in mind.

“Have we hit the breaking point with oncology drug prices? Some see the upward trend in cancer drug costs as accelerating — and unsustainable. Value-based pathways might rearrange the incentives to put some downward pressure on prices.”
When adult patients with obstructive sleep apnea (OSA) or narcolepsy are struggling with excessive daytime sleepiness (EDS),

**ONCE-DAILY SUNOSI** is the first and only WPA proven to improve wakefulness through **9 HOURS**

---

**INDICATIONS AND USAGE**

SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

**Limitations of Use:**

SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

**WARNINGS AND PRECAUTIONS**

**Blood Pressure and Heart Rate Increases**

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

 Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

 Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

**Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.**

**Psychiatric Symptoms**

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

 Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

 Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

 Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

**MOST COMMON ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

---

**Please see Brief Summary of full Prescribing Information on next page.**

**References:**


2. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.
SUNOSI® (sobrilametof) tablets, for oral use, CIV
BINDS® SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information for complete product information.
Initial U.S. Approval: 2010
INDICATIONS AND USAGE
SUNOSI is indicated for sleep-related respiratory events in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use
SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure [CPAP]) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities.

DOSE AND ADMINISTRATION
Important Considerations Prior to Initiating Treatment
Prior to initiating treatment with SUNOSI, ensure blood pressure is adequately controlled. General Administration Instructions
Administer SUNOSI orally upon awakening with or without food. Avoid taking SUNOSI within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.

SUNOSI 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.

CONTRAINDICATIONS
SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of MAO inhibitors.

WARNINGs AND PRECAUTIONS
Blood Pressure and Heart Rate Increases
SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the baseline value and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI). Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and hypertension disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction or other appropriate medical intervention consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms
Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorder.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Patients treated with SUNOSI should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of this label:
• Blood Pressure and Heart Rate Increases
• Psychiatric Symptoms

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug may not reflect the rates observed in practice. The safety of SUNOSI has been evaluated in 930 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 7.5 mg (OSA only), 75 mg, and 150 mg oral daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

Most Common Adverse Reactions
The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of SUNOSI than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia.

Table 1 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the narcolepsy population.

Table 1: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy (75 mg and 150 mg)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Narcolepsy</th>
<th>Placebo N = 118 (%)</th>
<th>SUNOSI N = 396 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased appetite</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia*</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Anxiety*</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache*</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea*</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Insomnia** includes insomnia, initial insomnia, middle insomnia, and terminal insomnia. “Anxiety” includes anxiety, nervousness, and panic attack. “Headache” includes headache, tension headache, and migraine headache.

Table 2 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the OSA population.

Table 2: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in OSA (75 mg, 75 mg, and 150 mg)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>OSA</th>
<th>Placebo N = 118 (%)</th>
<th>SUNOSI N = 235 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased appetite</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Anxiety</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain*</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Chest discomfort</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Hyperhidrosis</td>
<td>0</td>
</tr>
</tbody>
</table>

*“Anxiety” includes anxiety, nervousness, and panic attack. “Nausea” includes nausea and vomiting.

Adverse Events in Pooled Placebo-Controlled Clinical Trials that Compared Doses of 7.5 mg, 75 mg, and 150 mg Daily of SUNOSI to placebo, the following adverse reactions were detected: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth (Table 3).

Table 3: Dose-Dependent Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy and OSA

<table>
<thead>
<tr>
<th>Placebo</th>
<th>SUNOSI 7.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache**</td>
<td>8</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Nausea**</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

**In OSA only.

**Headache** includes headache, tension headache, and head discomfort. “Nausea” includes nausea and vomiting.

Adverse Reactions Resulting in Discontinuation of Treatment
In the 12-week placebo-controlled clinical trials, 7% of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of 930 patients (0.1%) who received placebo. Two adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anemia (2/396 [0.5%]), palpitations (2/396 [0.5%]), and restless leg syndrome (2/396; 0.5%).

Improvement in Blood Pressure and Heart Rate
SUNOSI’s effects on blood pressure and heart rate are summarized below. Table 4 shows maximum mean changes in blood pressure and heart rate recorded at sessions where the Maintenance of Wakefulness Test (MWT) was administered. Table 4 summarizes 24-hour ambulatory blood pressure monitoring (ABPM) and ambulatory heart rate monitoring performed in the outpatient setting.
drug ADVERSE REACTIONS in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI. Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI. Patients with moderate or severe renal impairment may be at a higher risk of MACE. Concomitant use of SUNOSI with other drugs that may increase the risk of a hypertensive reaction. Potential outcomes include heart attack, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

**Drug Interactions**

Monamine Oxidase (MAO) Inhibitors Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI therapy. Concomitant use of MAOIs and dopaminergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include heart attack, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

**Dopaminergic Drugs**

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors may increase blood pressure and heart rate. Patients should be monitored for increases in blood pressure and heart rate. See SUNOSI Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

**Use in Specific Populations**

**Pregnancy**

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUNOSI during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at www.SunosiPregnancyRegistry.com.

Available data from case reports are not sufficient to determine drug-associated risks of maternal birth defects, miscarriage, or adverse maternal or fetal outcomes. In a limited number of reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicity and fetal skeletal malformations and increased maternal drug levels. At doses 5 times the MRHD, it caused fetal fetal weight. The no-adverse-effect level for malformation and fetal toxicity is 5 times the MRHD.

**Lactation**

There are no data available on the presence of solriamfetol or its metabolites in human milk. The effects on the breastfed child after a single dose of this drug in milk are unknown. Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition.

**Contraindications**

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

**Pediatrihc Use**

Safety and effectiveness in pediatric patients have not been established. Clinical studies of SUNOSI in pediatric patients have not been conducted.

**Geriatric Use**

The total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (12/913) were 65 years of age or over. No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients in these clinical trials.

SUNOSI is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted to avoid toxicity in elderly patients. See Clinical Pharmacology: Effect of Age and Gender (Page 22) for further information.

**Clinical Pharmacology:**

**Effect of Age and Gender**

Data from controlled clinical trials and from literature on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

**Renal Impairment**

Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m²). Dosage adjustment is recommended for moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m²). SUNOSI is not recommended for patients with end stage renal disease (eGFR ≤15 mL/min/1.73 m²).

**Drug Abuse and Dependence**

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse SUNOSI has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of SUNOSI 300 mg, 600 mg, and 1200 mg (two, four and eight times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg (a Schedule IV controlled substance). A human abuse potential study in patients with the abuse potential of SUNOSI was conducted in the narcolepsy and obstructive sleep apnea (OSA) populations. SUNOSI was also evaluated during the two-week safety-follow-up periods in the Phase III studies. There was no evidence that SUNOSI produced adverse effects on cognitive function and behavior compared to placebo. SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

**Oversedage**

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. In overdose, supportive care should be managed with primarily supportive care, including cardiovascular monitoring. Consult a Certified PoisonControl Center at 1-800-222-1222 for latest recommendations.

**Patient Counseling Information**

Advise the patient to read the FDA-approved patient labeling (Medication Guide). For patients, use the Patient Information Wallet Card to convey the importance of discontinuing SUNOSI use if they are pregnant or plan to become pregnant.

Advises patients that SUNOSI is a controlled substance because it has the potential for abuse. Advise patients not to abuse SUNOSI. SUNOSI is a controlled substance (Schedule IV) under the Controlled Substances Act of 1970. The Controlled Substances Act makes it unlawful to prescribe, sell, distribute, administer or trafﬁc in any manner this drug, even once, to achieve a desired psychological or physiological effect. SUNOSI is a controlled substance because of its abuse potential.

**Blood Pressure and Heart Rate Increases**

Prescribe patients that SUNOSI can cause elevations of their blood pressure and pulse rate and that they should be monitored for such effects.

**Breast feeding**

Instruct patients to contact their healthcare provider if they experience, anxiety, irritability, agitation, or signs of psychosis or bipolar disorders.

**Lactation**

Monitor breastfed infants for adverse reactions such as agitation, insomnia, anorexia, and reduced weight gain.

**For more information, visit www.SUNOSI.com**

Developed by: Jazz Pharmaceuticals, Inc. Palo Alto, CA 94304

Protected by U.S. patent numbers: 8440715, 8877806, and 9604917

© 2020 Jazz Pharmaceuticals Inc., a subsidiary of Jazz Pharmaceuticals plc, all rights reserved. US-SOL-2000229 Rev04 3/2020

---

**Table 4: Mean Change in Baseline Blood Pressure and Heart Rate Assessed at MWT Sessions from Baseline Through Week 12: Mean (95% CI)**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg</th>
<th>SUNOSI 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>51</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>(0.7, 6.4)</td>
<td>(0.6, 6.5)</td>
<td>(1.7, 8.3)</td>
<td>(3.2, 10.3)</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>47</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>(0, 2.1)</td>
<td>(2, 4.2)</td>
<td>(1.5, 6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>58</td>
<td>26</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>(0, 1.4)</td>
<td>(2, 7.3)</td>
<td>(1.9, 7.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 5: Blood Pressure and Heart Rate by 24-Hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 12**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>SUNOSI 37.5 mg</th>
<th>SUNOSI 75 mg</th>
<th>SUNOSI 150 mg</th>
<th>SUNOSI 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>46</td>
<td>44</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>(0, 2), 2</td>
<td>(1, 4)</td>
<td>(1, 4)</td>
<td>(0, 6)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>46</td>
<td>43</td>
<td>49</td>
<td>96</td>
</tr>
<tr>
<td>(0, 1.9)</td>
<td>(0, 2.9)</td>
<td>(0, 2.9)</td>
<td>(0, 2.9)</td>
<td></td>
</tr>
</tbody>
</table>
With accelerated approval pathway, risk of withdrawal looms

The FDA’s accelerated pathway gets drugs to market quickly, but it also can mean patients are put on therapies that do not actually provide a clinical benefit.  

by JARED KALTWASSER

For many patients a cancer diagnosis can feel like the start of a timer. When will the test results come back? How quickly can I initiate therapy? How long do I have to live?

In some types of cancer, the timer feels especially short. Donna R. Cryer, J.D., president and CEO of the Global Liver Institute, says many patients with liver cancer already have advanced disease by the time they are diagnosed.

“There’s a very short time frame to be able to utilize any (treatment) option, let alone be able to find the best option,” Cryer says.

The number of treatment options has been growing, thanks in part to the creation of the Accelerated Approval Program at the FDA in 1992. As revised in 2012, it allows the agency to approve therapies based on “surrogate end points” that are, as the name suggests, substitutes for clinical outcomes, although they are supposed to correlate with them. The pathway is restricted to therapies that treat serious conditions and fill unmet medical needs.

But the wave of withdrawals had already started. In February, AstraZeneca withdrew the indication for Imfinzi (durvalumab) as a treatment for previously treated locally advanced or metastatic bladder cancer in adults. In March, Genentech said it was withdrawing the indication for Tecentriq (atezolizumab) as a treatment for metastatic urothelial carcinoma that had previously been treated with platinum-based chemotherapy agents, and Merck withdrew Keytruda’s indication as a treatment of patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Andrew Powaleny, a spokesperson for the trade group Pharmaceutical Research and Manufacturers of America, says the pathway has worked well, noting that therapies approved under the program “must meet the same standards of safety and efficacy for approval as all other medicines.” If a drug cannot prove its worth in confirmatory trials, he noted, they risk losing the indication.

Critics of accelerated approval

“Their’s a very short time frame to be able to utilize any (treatment) option, let alone be able to find the best option.”

—DONNA R. CRYER, J.D., PRESIDENT AND CEO OF THE GLOBAL LIVER INSTITUTE
say the problem is that the drug companies have been slow to produce data from confirmatory trials. In a report released in April, the Institute for Clinical and Economic Review, a drug-pricing think tank based in Boston, said the pathway’s performance has been mixed. “Although the FDA can fine companies or withdraw approval to penalize noncompliance with postmarketing requirements, it acts with significant restraint in deploying these measures,” the report stated. ICER pointed to Sarepta Therapeutics’ Exondys 51 (eteplirsen), a high-cost therapy for Duchenne muscular dystrophy, as an example. It was given accelerated approval in five years. Some private insurers have refused to cover the drug because of doubts about its efficacy. As of the April report, the company had yet to produce confirmatory data; the FDA has set a 2021 deadline for it to do so.

Philosophies vary as to when and why the FDA should withdraw indications and whether it should err on the side of safety or on the side of patient access. Cryer, who advocated for Opdivo’s continued use as a treatment for hepatocellular carcinoma, said she was “incredibly disappointed” by the decision, which she felt did not adequately consider the patient perspective. “That’s just sort of basic psychology: You don’t really know what you would or could tolerate and what you would or could trade off until you’ve gone through it,” she says. “And so that, that lived experience, is so, so important.”

In its report, ICER outlined 10 potential policy reforms it said would improve the accelerated pathway, including increasing enforcement, creating an annual review process and adding a label alert to the patient materials to make sure patients know the therapy was approved under the accelerated pathway.

Cryer believes the accelerated approval pathway could be improved by adding more patient voices to review committees. She says the risks associated with speedy approval are outweighed by the benefits of getting new treatment options to patients as quickly as possible.

“Our perception is that they’re striving for perfection in the midst of complexity,” she says. “And that has a risk.”

Jared Kaltwasser, a regular contributor to Managed Healthcare Executive®, is a freelance writer in Iowa.

Interested in more content like this? Subscribe to our newsletters!

Using your smartphone camera, hover over the QR code.
Biomarker-Driven Therapy Advances in NSCLC

Non-small cell lung cancer (NSCLC) represents approximately 85% of lung cancers in the world. The identification of predictive biomarkers and availability of potent agents have paved the way for a progressive era in early-stage NSCLC treatment. In a recent video interview, Paul K. Paik, M.D., clinical director of Thoracic Oncology Service at Memorial Sloan Kettering Cancer Center in New York City, noted that although chemotherapy is beneficial, biomarker testing gives physicians the ability to target a specific mutation and potentially optimize outcomes. This article highlights key points from the interview.

Biomarker-Driven Treatment With Targeted Therapy

Approximately 75% of patients with NSCLC have a targetable mutation (e.g., EGFR, KRAS, ALK, RET, ROS1, etc.), according to Paik. He advises that all patients be tested for biomarkers upon diagnosis using next-generation sequencing so physicians can accurately pursue the best therapy. Several distinctive biomarkers have been discovered and multiple approved, Paik said, and he further noted that response to therapies based on biomarker testing often exceeds chemotherapy and chemoinmunotherapy.

In concert with innovations in biomarker testing, the development of targeted therapies has “led to a dramatic extension in overall survival (OS) in patients with stage 4 lung cancer,” Paik noted. “This will soon reflect early-stage lung cancers as well.” To choose a targeted therapy for a patient, one must review responses and OS rates from clinical trials evaluating agents targeting the same type of mutation the patient has, Paik observed. For elderly patients who aren’t represented in said trials, other elements need to be considered (e.g., tolerability).

METs in NSCLC

One of the newer biomarkers that has been identified, MET exon 14 skipping, is caused by alterations in “junk” DNA segments between coding sequences that lead to deletion/skipping of exon 14, which is regulatory for the cell to recognize and control METs. “METs have not been targeted well until fairly recently,” Paik said. “These genes are activated in unregulated cancer growth and cell division, spreading cancer to other sites of the body.” The patient characteristics associated with MET exon 14 skipping are different from those of other biomarker-defined patients with NSCLC. Paik explained that these patients may be in their 80s and are equally proportioned smokers and nonsmokers; they may be frailer and have other medical conditions, so physicians should be cautious when assigning targeted therapies.

Approved therapies for MET exon 14 skipping for the treatment of NSCLC are Tabrecta (capmatinib) and, most recently, Tepmetko (tepotinib). Approved under accelerated approval by the FDA in 2021, Tepmetko is indicated for the treatment of adult patients with NSCLC harboring MET exon 14 skipping alterations. The approval was based on results from the VISION trial, a phase 2, single-arm, randomized study designed to test Tepmetko against the growth and spread of NSCLC. Patients with any type of NSCLC or asymptomatic brain METs could participate. The primary end point was overall response rate (ORR), and a secondary end point of note was progression-free survival (PFS). ORR was approximately 46% to 47%, and PFS was approximately nine months. The safety findings were similar to those of other MET inhibitors, with the main side effect being peripheral edema in 60% of patients.

Paik has found that the drug is well tolerated and that all patients had some degree of durable tumor shrinkage. He further noted that if MET exon 14 skipping was found at the beginning of testing, he would prescribe Tepmetko. If found later, he would prescribe it after patients had progressed on their initial therapy.

According to Paik, the approval of Tepmetko is an important step in targeting METs in NSCLC. “We are at the beginning of figuring this out for MET exon 14 skipping,” Paik said.

Paik predicts that within the next five years, targeted testing will shift away from DNA to show how alterations affect cancer biology and that new targeted therapies will develop.

REFERENCES

Let’s Connect.

Managed Healthcare Executive® is on LinkedIn!

Network with fellow executives from across the world while you stay current on healthcare’s new developments and innovations.

Follow Us

managed healthcare executive
Enrolling in a Medicare Advantage (MA) plan can ring up big health care savings for seniors, results of a recent study by UnitedHealth Group show. Using industrywide data from Milliman, the actuarial and consulting firm, the health services company found that those enrolled in an MA plan save, on average, 40% in annual premiums and out-of-pocket costs, or roughly $2,000 a year, compared with beneficiaries in the traditional Medicare.

The findings indicate, for example, that a 73-year-old individual in average health in 2020 would have spent $3,558 annually for MA coverage compared with $5,361 for traditional Medicare along with a Medicare Part D prescription drug plan. If the person also had purchased Medigap coverage, the cost would have risen to $5,992. It’s not surprising that a UnitedHealth Group study would champion MA coverage. The company is the largest MA plan provider, by enrollment, with a 26% market share, according to the Kaiser Family Foundation (KFF).

The popularity of MA has surged in the past decade as baby boomers swell the ranks of those covered by Medicare. Enrollment more than doubled from 2010 to 2020, according to a tally kept by KFF: 11 million seniors were enrolled in MA plans in 2010 compared with 24 million a decade later. Those 24 million account for almost 40% of Medicare beneficiaries.

David Muhlestein, chief strategy and chief research officer at Leavitt Partners, a health care consulting firm, cautions against an overly rosy picture of MA. Because of the differences between MA and traditional Medicare, calculating cost savings “isn’t apples to apples in terms of benefits for most beneficiaries,” he says. Additionally, many MA plans have narrow networks, so beneficiaries run the risk of having to go out of network to get required care, he notes. Muhlestein also points out that the government pays MA plans about 2% more per enrollee than it does for those enrolled traditional Medicare.

The UnitedHealth Group study also includes state-by-state comparison. In states such as Florida, where competition is fierce and half the Medicare beneficiaries are enrolled in MA plans, savings average 57% when compared to Medicare fee for service, according to UnitedHealth’s numbers. On the other end of the spectrum, only 4% of Medicare beneficiaries are enrolled in MA plans in Wyoming, and the savings average just 19%.

The companies selling MA coverage argue that the benefits go beyond dollar savings. Those with MA coverage receive “coordinated care, ensuring Medicare Advantage members have the access they need, while keeping overall health care spending down,” says Lambert van der Walde, executive director of UnitedHealth’s Center for Health Reform & Modernization.

The Better Medicare Alliance, a research and advocacy group for MA funded by insurers, released a study in March that had similar findings to the one conducted by UnitedHealth. The alliance’s study used 2018 Medicare Current Beneficiary Survey data to show that MA enrollees saved 40% in premium and out-of-pocket costs compared with people in traditional Medicare ($3,354 versus $4,994).

Susan Ladika is an independent journalist in Tampa, Florida, who covers healthcare and business.
Chronically and critically ill patients often need acute care after their stay in an intensive care or medical/surgical unit. While these medically complex patients make up a small part of overall care delivery, it is critical to identify the appropriate care setting for them in order to decrease the risk of costly rehospitalization.

Kindred Hospitals deliver efficient care through specialized programs that improve outcomes and patient satisfaction. Our physician-led interdisciplinary teams help reduce avoidable readmissions and guide patients home or to a lower level of care.

Visit kindredmanagedcare.com to request a conversation about how Kindred Hospitals’ level of service can help manage your critically complex patients.

Daily Physician Oversight • ICU/CCU-Level Staffing
ACO Expertise • Disease-Specific Certification from The Joint Commission
Oscar and Bright Health, with their retail orientation, are attracting investment, adding members, entering partnerships and making acquisitions. by SUSAN LADIKA

With their heavy reliance on technology and consumer-friendly focus, newer health insurance companies such as Oscar Health and Bright Healthcare are striving to upend traditional health insurers, attracting billions in investment funding in the process.

“They have a much more well-developed digital platform compared to existing insurers,” says Katherine Hempstead, senior policy adviser at the Robert Wood Johnson Foundation. With it, she adds, they are “trying to improve the game.”

The relatively new players in the health insurance market offer “a retail-like experience for members” and primarily operate in the individual and Medicare Advantage markets, says Tom Cassels, president of Rock Health, a venture fund focused on digital health. “Their websites are slick, airy and appealing, he says. “They are very different from the mainline incumbents, such as UnitedHealthcare (UHC) or Anthem, Cassels says. “They’re the next-generation, consumer-friendly plans.”

Boris Khey-Kheyfets, senior manager at the consultancy Deloitte, says the companies “have invested significantly in creating a superior customer experience” and strive to steer consumers to the appropriate site of care — whether that care is delivered in person or remotely. That has left some traditional insurers asking if they can replicate some of these capabilities or license some of these capabilities,” Khey-Kheyfets says.

Oscar has teamed up with Cigna to offer insurance for small businesses in an attempt to unite Cigna’s extensive provider networks and Oscar’s customer-service focus. Those small group plans are available in parts or all of four states: California, Connecticut, Georgia and Tennessee.

In April, Oscar announced it was launching +Oscar as a way to sell its full-stack technology platform to other payers and providers. The move opens the possibility of Oscar becoming as much a technology vendor as a health insurer. The pitch from Oscar is that +Oscar will deliver “end-to-end health plan services with the administrative efficiency of far larger health plans” and let smaller provider-sponsored and regional health plans “overcome scale disadvantages and lower administrative spend, driving improved profitability.”

Oscar, Bright Health and some of the other newcomers are bringing some sparkle to what remains a rather staid part of the healthcare sector. Their shiny new thingness can lead to some loss of perspective. The UHCs, Aetnas and Cignas have millions of members and billions in revenues. Oscar and Bright Health, which are the largest of the new entrants, have about a half-million members each.

Finding their niches
Oscar, which has gotten the most buzz, was launched in 2012. One of its co-founders is Joshua Kushner, the younger brother of Jared Kushner, the son-in-law and former senior adviser of former President Donald J. Trump.

“Oscar came out of the gate with a different business model,” appealing directly to consumers, Hempstead says. “Their websites are slick, airy and appealing, he says. “They are very different from the mainline incumbents, such as UnitedHealthcare (UHC) or Anthem, Cassels says. “They’re the next-generation, consumer-friendly plans.”

Oscar, Bright Health and some of the other newcomers are bringing some sparkle to what remains a rather staid part of the healthcare sector. Their shiny new thingness can lead to some loss of perspective. The UHCs, Aetnas and Cignas have millions of members and billions in revenues. Oscar and Bright Health, which are the largest of the new entrants, have about a half-million members each.
Individual plans are now available in almost 300 counties in 18 states, including New York, California and Texas. Nearly 530,000 consumers have signed up for coverage this year. 

Oscar tends to offer plans in urban areas when it enters a state, expanding to suburban and then more rural regions as it builds its network of providers, says Alessa Quane, the company’s executive vice president and chief insurance officer.

Starting this year, the insurer is also offering virtual primary care with $0 copays. “In a year when people didn’t go out very much, there’s certainly something to be said for having that option,” Quane says. The virtual primary care is offered by both English-speaking and Spanish-speaking providers, and almost 40% of patient utilization came from Spanish speakers. The payer has found members with chronic conditions have been more likely to use virtual primary care. Adherence to recommended care has been high, with consumers filling 80% of prescriptions and providers having received a member satisfaction score of 99%.

Another new company entering the individual insurance market is Friday Health Plans, founded in Denver in 2015. It is small compared with Oscar and Bright Health, having only 70,000 members. Most of Friday Health’s plans offer primary care visits, mental health counseling, telehealth visits and generic drugs at no cost to members. Friday Health acquired Colorado Choice, a local health plan, to test its concept, says its CEO, Sal Gentile. Since its initial success, Friday has expanded into three other Western states, offering plans in the small group as well as the individual market. Like many smaller businesses in sectors dominated by larger companies, Friday Health prides itself on offering, in Gentile’s words, “high-touch customer service,” and the company says it picked its name because it wants to be “the Friday of health insurance — consistent, dependable and a breath of fresh air.” Gentile says the company works to solve its members’ problems in just one phone call. 

Although the major insurers have reentered or expanded their presence in the individual market in 2021 after previously pulling out or reducing their efforts, Gentile says he thinks Friday’s focus on that niche gives them an advantage.

Bright Health, which also sells coverage in both the individual market and Medicare Advantage, was co-founded in 2016 by the former CEO of UHC, Bob Sheehy. He told CNBC in 2018 that after UHC pulled out of most of the individual market, he “started the company with a vision to catalyze the individual marketplace.”

Bright Health is now selling plans in 50 markets in 13 states. The Minneapolis-based payer also owns about 40 primary care clinics and says it provided care to more than 220,000 patients either in person or virtually last year.

This year, Bright Health has gone on a bit of an acquisition spree. In January, it announced it was planning to acquire Central Health Plan of California, which serves 110,000 Medicare Advantage members. In April, it acquired Zipnosis, a telehealth platform provider. Financial terms of the deal were not disclosed.

Investors are showing some confidence in these new insurers. In April, Friday Health announced it had signed an agreement to receive $100 million in equity investment and $60 million in debt financing. Friday Health’s membership grew by more than 400% from 2020 to 2021, and the insurer will use the additional funding to expand to new markets. Gentile says, with plans to expand to three to five states each year.

Google’s parent company, Alphabet, invested $375 million in Oscar in 2018. When it went public in March, Oscar priced its shares at $39 and the price had dropped to $34.80 when the market closed. The market hasn’t been too kind to Oscar since. The share price has been on a downward trajectory so far, falling into the $20-$25 range. Still, its market capitalization is north of $4 billion.

Bright Health is preparing for its own IPO. According to the company’s June 15 Securities and Exchange Commission filing, it plans to sell 60 million shares at $23 per share, which would raise about $1.3 billion.

“T’m kind of glad they’re doing IPOs,” Hempstead says of Oscar and Bright. “It’s easy to imagine them being acquired” by a traditional insurer otherwise. IPOs “are better for competition,” she says. “I think it’s better for the market.”

Susan Ladika is an independent journalist in Tampa, Florida, who writes about business and healthcare.
Specialists are testing the value-based care waters

After having thrived in a fee-for-service healthcare system, can chronic disease specialists be enticed to switch?

Specialists are key partners for delivering value-based care, particularly for patients with chronic diseases. This involves the appropriate diagnosis of conditions, including rare diseases, stewardship of diagnostics and value-based prescribing for specialty medications.

Lawrence Kosinski, M.D., MBA, founder and chief medical officer of SonarMD, a tech-enabled care coordination solution for digestive health, notes the great majority of high per-capita cost of care comes from specialists’ orders.

“Right now, most specialty value-based care programs focus on procedure episodes like hip or knee surgery,” he says. “But specialists also care for patients with complex, chronic medical conditions, and this care accounts for $220 billion in healthcare spending annually — not including the fast-growing specialty pharma expense.”

A large proportion of that cost is variable. For example, among gastrointestinal (GI) diseases, inflammatory bowel disease (IBD) drives more than half the total variable cost. That’s an indicator that there’s an opportunity to better manage those patients with IBD through value-based care arrangements.

“If clinical and financial incentives are aligned, specialists would be further incentivized to keep patients out of acute-care settings, lowering the overall cost of care and improving quality of life for patients with chronic disease,” Kosinski says.

A major challenge is that many chronic conditions do not have current published clinical pathways. “The care is provided in a reactive fashion, as it is dependent upon a patient recognizing symptom deterioration,” observes Kosinski. “Unfortunately, they often don’t detect this deterioration until a hospital visit is necessary.”

Additionally, specialists typically do not have a financial incentive to proactively manage complex care or specialty formulary costs. Many specialists have thrived in a healthcare system geared toward fee for service, which rewards doing procedures and sometimes writing a prescription. The stakes are higher now with specialty drugs making up an increasing proportion of total drug expenditures. Kosinski ticks off some ways to infuse more value into healthcare: aligning payer and provider incentives with the best outcomes for the lowest possible costs, deploying technology to make efficient use of whatever resources are at hand and getting patients vested in their healthcare.

Keith Boell, D.O., chief quality officer for population initiatives at Geisinger, a healthcare system and health plan headquartered in Danville, Pennsylvania, says the industry has been slow to get specialists involved in value-based care.

“Specialists can help influence the care of patients across a large geographic footprint, including patients they may not see in their clinics,” he says. “When the majority of reimbursement is fee for service, specialists are incentivized to focus on patients in their clinics and may not become as engaged in the broader population health discussion.”

Distance can be a major barrier for some patients. Many specialists practice in large, multispecialty practices, frequently at academic medical centers, requiring patients to travel from their local communities. Many people in and out of healthcare see telehealth solving that problem.

Getting tech involved

Good patient outcomes have served as the most convincing argument for physicians to accept value-based care strategies. In addition, creating a transparent and representative physician leadership that the medical staff has confidence in is of critical importance. It is essential to have a forum to allow rapid dissemination of information.

Continued on page 52
The Pharmacy Benefit Management Institute® (PBMI®) is excited to announce the 2021 PBMI® Annual National Conference will be hosted in Orlando, Florida from September 13-15, 2021, at the JW Marriott, Orlando, Grande Lakes.

This year’s conference will offer a unique hybrid experience, comprised of a world-class meeting in Orlando along with an interactive virtual offering. Throughout the three-day event, you’ll hear from companies operating across the PBM Industry including CVS Health, Biologics by McKesson, WellDyne, Capital Rx and more.

Announcing PBMI®’s 2021 Keynote Speaker

Scott Gottlieb, MD
Dr. Gottlieb’s work focuses on advancing public health through developing and implementing innovative approaches to improving medical outcomes, reshaping health care delivery, and expanding consumer choice and safety. He is a resident fellow at the American Enterprise Institute, a member of the board of directors of drug maker Pfizer, a member of the board of directors of the biotech company Illumina, a contributor to the cable financial news network CNBC, and a partner at the venture capital firm New Enterprise Associates.

Key Topics of Discussion:

» Contracting & Industry Relations
» Innovation & Technology
» Clinical & Trend Management
» Designing the Drug Benefit
» Best Practices in Care Management Strategies
» Best Practices in Cost Containment
» Quality Improvement

Reasons to Attend:

» Opportunity to earn continuing education credits
» Learn real-world strategies for cost containment, workflow efficiency, and quality improvement
» Expand your network with pharmacy benefit management veterans, decision-makers, and potential partners
» Participate in the inaugural PBMI® Innovation Challenge

REGISTER TODAY!
Scan or visit:
events.pbmi.com/Annual-National-Conference

In Partnership with
Specialists are testing the value-based care waters

“But gastroenterologists must also think beyond colonoscopies and endoscopies to consider more integrated care management for patients with chronic conditions.” — LAURENCE KOSINSKI, M.D., MBA, FOUNDER AND CHIEF MEDICAL OFFICER OF SONARMD

Continued from page 50

and to exchange feedback. Technology can play a critical role in encouraging this coordination.

Daniel Hommes, M.D., a gastroenterologist who has worked and published extensively in value-based care, notes specialists offer a higher chance of achieving better clinical outcomes and patient experiences at lower cost. An example would be if their clinical network is delivering on Healthcare Effectiveness Data and Information Set quality measures tied to financial incentives and bonus structures. “The biggest challenge is getting a technology infrastructure in place that can facilitate providers (with offering) value-based care since traditional EMR systems do not offer this,” he says.

SonarMD’s IBD solution can leverage technology to facilitate patient engagement and care coordination while driving financial and clinical alignment with payers. “This was especially helpful during the pandemic to ensure patients were proactively engaged and the care team could catch flare-ups before hospitalization was required,” Kosinski says. “Our work with these practices is contracted through Horizon Blue Cross Blue Shield of New Jersey, so physicians are paid to proactively manage IBD, and Horizon Blue Cross can share in savings from the program.”

A value-based care strategy

At Geisinger, specialists are involved in several value-based care initiatives. One is a program called “Lower GI Flag,” a collaboration between Geisinger and Medial Early- Sign that uses machine learning to identify patients at the highest risk for colorectal cancer who are overdue for screenings.

“We can do targeted outreach to get those patients scheduled for a colonoscopy,” Boell says. “Additionally, advanced endoscopy services can help patients avoid higher cost settings, including the operating room.”

Because gastroenterologists spend the majority of their time doing colonoscopies for screening and surveillance of colon polyps, which have little variation in cost, these procedures should be bundled into 14-day episodes, which would bring gastroenterologists into the value chain, Kosinski says.

“But gastroenterologists must also think beyond colonoscopies and endoscopies to consider more integrated care management for patients with chronic conditions,” he continues. “This is an opportunity to broaden their financial model and keep patients in their practices instead of in acute care settings.”

Tonny M. Lee, M.D., medical director of the GI laboratory and chair of the Gastroenterology Division at Providence Little Company of Mary Medical Center in Torrance, California, says as healthcare delivery continues to evolve on both regional and national levels, health systems must also strive to meet new and expected standards.

With that in mind, great efforts have been implemented to achieve the goals of value-based care, including enhancing patient experiences, elevating providers’ clinical experience and serving unique needs of various communities. To meet these demands, the hospital has created clinical institutes across eight specialties. “The clinical institute model differentiates Providence from other health systems by pulling on the expertise across our 11-hospital region to share latest findings, treatment options and any advances through research,” says Lee. For example, physician leaders have met on a routine basis to share clinical concerns and establish consensus guidelines for acute GI hemorrhage management, colorectal cancer prevention and approaches to treating patients with irritable bowel syndrome and IBD, he says. “The clinical institute model has facilitated a free exchange of ideas among surgeons, radiologists, oncologists and gastroenterologists, fostering a stronger bond and camaraderie on a personal level, observes Lee. Patients are less likely to seek care academic medical centers as a result. Ultimately, the efforts lead to better access and outcomes and improved patient satisfaction.

Physician engagement continues to be an issue, though, as the system’s goals and those of independent specialists often do not completely align, Lee continues. Educating clinicians to recognize the value of quality over quantity remains a top priority. The disruption of healthcare caused by the COVID-19 pandemic and a renewed interest in preventive care may help push them along.

Many health systems are banking on value-based care, now and in the future, Lee says. It’s an opportune time for specialists to get involved and join the trend, he says: “By adopting value-based care, specialists not only can achieve the Holy Grail of improved patient care but also can potentially enhance financial rewards by shared savings and other revenue enhancements.”

Keith Loria is a freelance writer in the Washington, D.C., area.
Get easy access to news, information, practice solutions, trusted perspectives through peer-based forums and opinions.

View in-depth interviews with industry experts.

Find healthcare management resources sorted by topic.

Medical World News®
Discover the 24-hour news channel for #healthcareprofessionals, by healthcare professionals.

Website Enhancements
- Streamlined, user-friendly navigation
- Improved mobile compatibility for easier viewing on phones
- Increased responsiveness and improved search capabilities
Managed Healthcare Executive

for an Enhanced Website Experience

Use our improved navigation and search.

Sign up to receive e-newsletters and the print publication.

Read keynote highlights, industry trends and policy updates.

Explore content relative to specific therapeutic areas or disease states.

Managed Healthcare®
The C-Suite Advisor EXECUTIVE

Medical World News®
Discover the 24-hour news channel for healthcare professionals, by healthcare professionals.
The busy signal: Telehealth deals surge as usage stays high

Insurers make acquisitions as pandemic adoption of virtual care delivery becomes the norm.  

As health insurers and retailers focus on meeting patients’ demands to have access to healthcare when they want it, how they want it, telehealth acquisitions and expansions are going strong.

Among the deals announced this spring were Cigna’s acquisition of MDLive, Bright Health’s acquisition of Zipnosis and Walmart’s announcement that it was planning to purchase MeMD. Meanwhile, Amazon, which has been offering telehealth services to some of its own employees, said it would start to offer virtual care nationwide and signed its first deal this spring to provide its Amazon Care telehealth app to another company.

The dealmaking is just one of the business-related symptoms of the surge of telehealth usage that started with the COVID-19 pandemic last year and has continued at a pace not seen in prior years.

Telehealth “needed a jolt. The jolt was the pandemic to really get adherence and adoption,” says Nick Donkar, U.S. health services deals sector leader at the consultancy PwC. COVID-19 “changed the industry. People realize telehealth is a better solution,” adds Pouria Sanae, founder and CEO of ixlayer, a San Francisco-based company that helps providers offer diagnostic testing virtually.

People have grown accustomed to getting online when they have a medical problem, notes Sanae. In the past, if an individual had symptoms of an illness, “their first reaction was to go see a doctor,” he says. Today, “their first reaction is to go to Dr. Google,” and then they may search out an online healthcare provider.

Because of COVID-19, telehealth usage soared by 154% during the last week of March 2020, as the pandemic was just beginning to take hold, compared to the same period in 2019, according to data compiled by the Centers for Disease Control and Prevention.

FAIR Health, a nonprofit health-care data analytics company, found that telehealth “claims lines” — the individual services or procedures listed on insurance claims — soared throughout 2020 for those covered by private insurance. Comparing December 2019 with December 2020, telehealth claims lines soared more than 2,800%. They represented just 0.22% of all medical claims lines in December 2019 compared with 6.51% in December 2020. Medicare and Medicaid claims are not included in the statistics.

Niche no more

Behavioral healthcare was the top reason for consumers to seek telehealth care, followed by seeking treatment because of possible exposure to “communicable diseases,” which FAIR Health says likely reflects possible exposure to COVID-19.

Telehealth usage has dipped this year, according to FAIR Health’s data. From February to March, the most recent month for which statistics are available, telehealth claim lines dipped 5.1%, but they still represent 5.6% of all claims.

“A lot of people want hybrid care,” with a blend of in-person and virtual healthcare, says Sari Kaganoff, general manager of consulting at Rock Health, a venture fund that focuses on digital health. Telehealth “isn’t a niche anymore. Everyone knows it’s the future,” she adds, which makes it very appealing to investors as well as consumers.

Last year, Cigna created a new brand called Evernorth for its health services portfolio. Before the pandemic, 97% of Cigna’s behavioral healthcare customers had never had a virtual visit with a provider, said Eric Herbek, Evernorth’s vice president of virtual care, via email. He also noted that since the pandemic began, 60% of behavioral health patients say they have continued using virtual care.

Continued on page 56
INOmax DSIR® PLUS DELIVERY SYSTEMS

Devoted to Delivering Ongoing Innovations in Critical Care

The INOmax DSIR® Plus Delivery Systems provide innovative design and user experience to support the ever-changing demands of the critical care space and keep patient safety a top priority.1,2

- Delivering specialized, redundant, and customizable alarm features designed to help mitigate the risk of device-related rebound pulmonary hypertension
- Advanced features enable delivery of therapy specifically for the MRI suite
- Integration with neonatal transport systems to support seamless delivery of therapy

Applications
The INOmax DSIR® Plus Delivery Systems deliver INOMAX® (nitric oxide) gas, for inhalation. The INOmax DSIR® Plus Delivery Systems must only be used in accordance with the indications, usage, contraindications, and warnings and precautions described in the INOMAX package inserts and labeling. The approved patient population is limited to neonates. Refer to the INOMAX Full Prescribing Information prior to use.

Device Warnings
- Abrupt discontinuation of INOMAX can lead to worsening oxygenation and increasing pulmonary artery pressure (rebound pulmonary hypertension syndrome). To avoid abrupt discontinuation, use the INOblender® or backup mode immediately to reinstate INOMAX therapy and refer to the INOMAX package insert.
- If the high NO alarm activates, the delivery system should be assessed for proper setup while maintaining INOMAX delivery.
- Do not connect items that are not specified as part of the system.
- If an alarm occurs, safeguard the patient first before troubleshooting or repair procedures.
- Use only INOMAX, pharmaceutical grade NO/N₂.

Use in an MR Environment
- Only use a size “88” (1,963 liters) cylinder that is marked “MR Conditional. Keep cylinder at 100 gauss or less.” with the DSIR® Plus MRI while in the scanner room. Use of any other cylinder may create a projectile hazard.

While you take care of patients, we remain dedicated to helping advance critical care.
Learn how at inomax.com/inomax-delivery-systems/device-innovation

INOMAX® (nitric oxide gas)
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure
INOMAX® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS
INOMAX is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOMAX. Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX therapy immediately.

Hypoxemia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMAX; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMAX to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO₂ concentration, or if the NO₂ concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO₂ analyzer should be recalibrated. The dose of INOMAX and/or FiO₂ should be adjusted as appropriate.

Worsening Heart Failure
Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMAX while providing symptomatic care.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMAX doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMAX, a result adequate to exclude INOMAX mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMAX and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMAX and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMAX than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents
Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE
Overdose with INOMAX is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO₂ levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMAX.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

INOMAX® is a registered trademark of a Mallinckrodt Pharmaceuticals company.

© 2018 Mallinckrodt. US-1800236 August 2018
The busy signal: Telehealth deals surge as usage stays high

Continued from page 53

Wheeling and telehealth dealing

As the healthcare system adjusted care delivery, there has been a tremendous amount of deal activity in the health services space, Donkar says, and much of that activity involves virtual care. The activity has been driven by healthcare companies’ abilities to leverage artificial intelligence, improve care and reduce costs using telehealth, he says.

Among the major deals:

- Cigna’s Evernorth brand completed its acquisition of MDLive in April. Cigna had previously been a major investor in the telehealth company, which is based in Miramar, Florida. Terms of the deal were not disclosed.

- Bright Health acquired Zipnosis, also in April. Both companies are based in Minneapolis. Zipnosis’ telehealth platform is used to power the virtual visits of almost 60 large health systems across the country. Details of the transaction were not disclosed. In May, Bright Health filed preliminary paperwork for its own initial public offering.

- Walmart in May announced it had reached an agreement to acquire MeMD, a telehealth provider based in Phoenix. With the acquisition, Walmart Health will be able to provide primary care, urgent care and behavioral healthcare — with the goal of “complementing our in-person Walmart health centers,” the retailer said in a recent press release.

Investors plowed $21.6 billion into digital health companies last year, according to Mercom Capital Group in Austin, Texas. The money came in as venture capital, debt and public market financing. Along with major companies such as insurers and retailers, “there’s a lot of money flowing into healthcare right now” from sources such as venture capital companies, Kaganoff says. Investment is “on a wave that’s rising,” she says. “It hasn’t crested yet.”

Other companies are taking different approaches to telehealth. Many eyes are on Amazon and its maneuvers. Amazon created Amazon Care in 2019 to provide virtual care to the online retailers’ employees and their families in Washington state and also offered in-person care at their employees’ homes with medical professionals doing such things as drawing blood or listening to a patient’s lungs. This spring, Amazon announced it was planning to expand its virtual care to Amazon employees around the country, as well as to other companies. It also is planning to expand its in-person care to cities such as Washington, D.C., and Baltimore.

According to several media reports, Amazon Care had signed up its first virtual care client, Precor, a fitness equipment company based in suburban Seattle, in May. Precor was acquired by Peloton in the spring.

Meanwhile, Walmart said in a press release that the acquisition of MeMD “reinforces Walmart’s commitment to integrated, omni-channel health delivery that leverages data and technology to improve engagement, health equity and outcomes.”

Kaganoff says the blend of online and in-person care should serve the retailer well. “Walmart has a really nice opportunity because of its physical footprint.”

The future of virtual care

Although telehealth has primarily been associated with urgent care delivery in the past, Cigna is convinced “virtual care can be used effectively to treat much more than strep throat or an ear infection,” Herbek wrote via email. “We see a future where (patients with diabetes) and others with chronic and complex care needs can access comprehensive care online and where their providers are part of a connected network of care.”

Herbek added that care provided through MDLive is intended to complement, rather than replace, consumers’ interactions with their current providers, with the goal of improving access to care and health outcomes.

Cigna plans to achieve that through earlier identification and diagnosis of critical care needs, improved medication management and increased affordability through referrals to high-quality providers, guidance to appropriate and affordable sites of care, and easier connections to affordable prescriptions, Herbek wrote.

Donkar says he expects to see a “continued interest in all things virtual” in the future.

Herbek agrees: “We see virtual care as an area of rapid innovation in the industry, pushing into new aspects of care and becoming a more essential ingredient in health plan benefit design.”

Susan Ladika is an independent journalist in Tampa, Florida, who covers business and healthcare.