DIGITAL THERAPEUTICS
There’s a new kid on the prescription pad

Also

Industry Analysis
Dollar General and the rural healthcare desert

Drugs in the Pipeline
Targeted NSCLC treatments

Conference Insider
Asembia’s 2021 Specialty Pharmacy Summit
For patients with Homozygous FH (HoFH) aged 12 years or older†

**EVKEEZA® powerfully reduced LDL-C levels by an average of ~50% as an adjunct to current LLTs**

*The LDL-C—lowering effect of EVKEEZA may be measured as early as 2 weeks. At week 24, the LS mean treatment difference between EVKEEZA and placebo in mean percent change in LDL-C from baseline was -49% (95% CI: -65% to -33%, P<0.001). LS mean percent change in LDL-C from baseline with EVKEEZA was -47% and with placebo was +2%.*

**INDICATION**
EVKEEZA® is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH).

**Limitations of Use:**
- The safety and effectiveness of EVKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined.

**IMPORTANT SAFETY INFORMATION**
**Contraindication**
EVKEEZA is contraindicated in patients with a history of serious hypersensitivity reactions to evinacumab-dgsc or to any of the excipients in EVKEEZA. Serious hypersensitivity reactions, including anaphylaxis, have occurred.

**Warnings and Precautions**
**Serious Hypersensitivity Reactions:** Serious hypersensitivity reactions have occurred with EVKEEZA. If signs or symptoms of serious allergic reactions occur, discontinue EVKEEZA infusion, treat according to the standard-of-care, and monitor until signs and symptoms resolve.

Visit EVKEEZAhcp.com to learn more about EVKEEZA
EVKEEZA® lowered LDL-C by ~50%, on average, at 24 weeks1

Calculated LDL-C LS mean percent change from baseline over time through week 241

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo + LLTs</th>
<th>EVKEEZA + LLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>-20</td>
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</tr>
<tr>
<td>24</td>
<td>-20</td>
<td>-20</td>
</tr>
</tbody>
</table>

EVKEEZA is a first-in-class FDA-approved monoclonal antibody that lowers LDL-C independently of LDLR activity.

At week 24, EVKEEZA lowered LDL-C by an average of 135 mg/dL from baseline in patients receiving EVKEEZA.

Study design

The efficacy and safety of EVKEEZA in the treatment of HoFH was demonstrated in a multicenter, double-blind, randomized, placebo-controlled study in patients with HoFH. The mean age of patients at baseline was 42 years (range: 12 to 75 years). Patients were on a background of LLTs, including maximally tolerated statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis. The mean LDL-C at baseline was 255 mg/dL. In the double-blind treatment period, 43 patients were randomized to receive EVKEEZA 15 mg/kg IV every 4 weeks and 22 patients to receive placebo. In the open-label treatment period, 64 patients received EVKEEZA 15 mg/kg IV every 4 weeks.1

The primary endpoint was percent change in LDL-C from baseline to week 24. At week 24, the LS mean treatment difference between EVKEEZA and placebo for ApoB and non-HDL-C was -49% (95% CI: -65% to -33%; P<0.0001). LS mean percent change in LDL-C from baseline with EVKEEZA was -47% and with placebo was +2%.1

A key secondary endpoint was the LS mean change in LDL-C from baseline to week 24. At week 24, the LS mean change in LDL-C from baseline for patients receiving EVKEEZA was -135 mg/dL compared with -3 mg/dL for patients receiving placebo (treatment difference -132 mg/dL; 95% CI: -175 to -89; P<0.001).1

At week 24, the LS mean difference between EVKEEZA and placebo for ApoB and non-HDL-C was -37% (95% CI: -49% to -25%; P<0.001) and -52% (95% CI: -65% to -39%; P<0.001), respectively.1,2

ApoB=apolipoprotein B; CI=confidence interval; DBTP=double-blind treatment period; IV=intravenous; non-HDL-C=non-high-density lipoprotein-cholesterol; PCSK9=proprotein convertase subtilisin kexin type 9; SE=standard error.

Lactation: There are no data on the presence of evinacumab-dgnb in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EVKEEZA and any potential adverse effects on the breastfed infant from EVKEEZA or from the underlying maternal condition.

Females and Males of Reproductive Potential: Consider pregnancy testing in patients who may become pregnant prior to starting treatment with EVKEEZA. EVKEEZA may cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use effective contraception during treatment and for at least 5 months following the last dose of EVKEEZA.

Pediatrics: The safety and efficacy of EVKEEZA have not been established in pediatric patients with HoFH who are younger than 12 years old.


IMPORTANT SAFETY INFORMATION (continued)

Embryo-Fetal Toxicity: EVKEEZA may cause fetal harm when administered to pregnant patients. Advise patients who may become pregnant of the risk to a fetus. Consider obtaining a pregnancy test prior to initiating treatment with EVKEEZA. Advise patients who may become pregnant to use effective contraception during treatment and for at least 5 months following the last dose.

Adverse Reactions

Common adverse reactions (≥5%) were nasopharyngitis (16%), influenza-like illness (7%), dizziness (6%), rhinorrhea (5%), and nausea (5%).

Use in Specific Populations

Pregnancy: EVKEEZA may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. If a patient becomes pregnant while receiving EVKEEZA, healthcare providers should report EVKEEZA exposure by calling 1-833-385-3392.

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

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EVK.2108.0002
08/2021
EVOKEEZA (evinacumab-dgnb) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

EVOKEEZA is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use:
- The safety and effectiveness of EVOKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with homozygous familial hypercholesterolemia (HoFH).
- The effects of EVOKEEZA on cardiovascular morbidity and mortality have not been determined.

4 CONTRAINDICATIONS

EVOKEEZA is contraindicated in patients with a history of serious hypersensitivity reaction to evinacumab-dgnb or to any of the excipients in EVOKEEZA. Severe hypersensitivity reactions, including anaphylaxis, have occurred (see Warnings and Precautions [5.1]).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Hypersensitivity Reactions

Serious hypersensitivity reactions have occurred with EVOKEEZA. In clinical trials, 1 (1%) EVOKEEZA-treated patient experienced anaphylaxis versus 0 (0%) patients who received placebo. If signs or symptoms of serious hypersensitivity reactions occur, discontinue EVOKEEZA infusion, treat according to the standard-of-care, and monitor until signs and symptoms resolve. EVOKEEZA is contraindicated in patients with a history of serious hypersensitivity reaction to evinacumab-dgnb (see Contraindications [4]).

5.2 Embryo-Fetal Toxicity

Based on the findings in animal reproduction studies, EVOKEEZA may cause fetal harm when administered to pregnant patients. Administration of evinacumab to rabbits during organogenesis caused increases in fetal malformations at doses below the human exposure. Advise patients who may become pregnant of the risk to a fetus.

Consider obtaining a pregnancy test prior to initiating treatment with EVOKEEZA. Advise patients who are pregnant to avoid exposure to evinacumab-dgnb during treatment with EVOKEEZA and for at least 5 months following the last dose of EVOKEEZA (see Use in Specific Populations [8.1, 8.3]).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity Reactions (see Warnings and Precautions [5.1])

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Safety data are based on pooled results from two randomized, double-blind, placebo-controlled trials that included 81 patients treated with EVOKEEZA. The mean age of EVOKEEZA-treated patients was 48 years (range: 15 to 75 years), 52% were women, 5% were Hispanic, 82% were White, 7% Asian, 3% Black, and 9% Other. Forty-five (54%) EVOKEEZA-treated patients had HoFH. Patients received EVOKEEZA as add-on therapy to other lipid-lowering therapies, including maximally tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and apheresis.

Adverse reactions led to discontinuation of treatment in 2 (2%) patients treated with EVOKEEZA, including 1 case of anaphylaxis, and 1 (2%) patient who received placebo. The most common adverse reactions (reported in greater than 3% of EVOKEEZA-treated patients and more frequently than in placebo) are shown in Table 1.

Table 1: Adverse Reactions Occurring in >3% of Patients Treated with EVOKEEZA and Greater than Placebo in 24-Week, Pooled, placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (N=54)</th>
<th>EVOKEEZA (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Influenza-like Illness</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Asthma</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Other adverse reactions occurring in less than 3% of patients treated with EVOKEEZA and greater than placebo included constipation, upper respiratory tract infection, nasal congestion, and abdominal pain.

Transient, mild to moderate decreases in diastolic blood pressure and increases in heart rate occurred in clinical trials of EVOKEEZA infusion but did not require intervention and resolved post-infusion.

Serious Hypersensitivity Reactions

Anaphylaxis was reported in 1 (1%) patient treated with EVOKEEZA and 0% in patients who received placebo. Infusion Reactions

Infusion reactions were reported in 6 (7%) patients treated with EVOKEEZA and in 2 (4%) patients who received placebo. The following infusion reactions occurred in EVOKEEZA-treated patients: infusion site pruritus, pyrexia, muscular weakness, nausea, and nasal congestion.

6.2 Immunogenicity

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

No patients developed treatment-emergent antibodies to EVOKEEZA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, EVOKEEZA may cause fetal harm when administered to pregnant patients. Available human data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Evinacumab-dgnb is a human IgG monoclonal antibody (see Description [11] in the full prescribing information), and human IgG is known to cross the placental barrier; therefore, evinacumab-dgnb has the potential to be transmitted from the mother to the developing fetus.

Subcutaneous administration of evinacumab-dgnb to pregnant rabbits during the period of organogenesis resulted in fetal malformations (demed head, hydrocephalus, and flexed limbs) at doses below the maximum recommended human dose (MRHD). No adverse embryofetal effects were observed with subcutaneous administration of evinacumab-dgnb to pregnant rats during the period of organogenesis at doses below the MRHD. Measurable evinacumab-dgnb serum concentrations were observed in fetal rabbit and rat sera at birth, indicating that evinacumab-dgnb, like other IgG antibodies, crosses the placental barrier (see Data). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

If a patient becomes pregnant while receiving EVOKEEZA, healthcare providers should report EVOKEEZA exposure by calling 1-833-305-5392.

Animal Data

In an embryo-fetal development study in pregnant rabbits, evinacumab-dgnb was administered subcutaneously at doses of 1, 5, 10, and 30 mg/kg every 3 days (Q3D) during the period of organogenesis from gestation day 7 to day 19. Evinacumab-dgnb was teratogenic in rabbits, causing deformed head, dilation of the lateral and third ventricles of the brain, and flexed fore/hind paws at maternal evincumab-dgnb dosages. This resulted in low human exposure at the MRHD of 15 mg/kg every 4 weeks, based on AUC. Other fetal malformations, consisting of irregular and abnormal ossification in the skull, palate, and metacarpal, and enlarged anterior and posterior fontanelles occurred and were consistent with significant maternal toxicity (including early deaths due to abortion and premature delivery at all doses, reduction in maternal body weight gains, and reduced maternal food consumption). There were no increases in post-implantation losses, resorptions, total (early, late, and late). and decreased fetal body weight were also consistent with maternal toxicity. Evinacumab-dgnb was present in the sera of fetuses born from mothers at 10 and 30 mg/kg/Q3D at levels or higher than in maternal serum.

In an embryo-fetal development study in pregnant rats, evinacumab-dgnb was administered subcutaneously at doses of 5, 10, 30, and 300 mg/kg/Q3D during the period of organogenesis from gestation day 6 to day 10. Maternal exposures to evinacumab-dgnb were below the human exposure measured at the MRHD. Evinacumab-dgnb resulted in unexplained maternal deaths at 100 mg/kg/Q3D. Evinacumab-dgnb crossed into the developing fetal circulation (fetal/maternal AUC B: 8.25 in T: 10.5 in). Maternal liver and placenta doses were below the maternal or fetal outcomes. Evinacumab-dgnb is a human IgG4 monoclonal antibody that is transmitted from the mother to the developing fetus. Based on the findings in animal reproduction studies, EVOKEEZA may cause fetal harm when administered to pregnant patients. Advise patients who may become pregnant of the risk to a fetus.

Consider pregnancy testing in patients who may become pregnant prior to starting treatment with EVOKEEZA (see Warnings and Precautions [5.1] and Use in Specific Populations [8.1]).

Contraception

Female

Based on animal studies, EVOKEEZA may cause fetal harm when administered to pregnant patients (see Use in Specific Populations [8.1]). Patients who may become pregnant should use effective contraception during treatment with EVOKEEZA and for at least 5 months following the last dose of EVOKEEZA.

8.2 Lactation

Risk Summary

There are no data on the presence of evinacumab-dgnb in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal inflammation and increased systemic exposure in the breastfed infant to evinacumab-dgnb are unknown.

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

8.3 Females and Males of Reproductive Potential

EVOKEEZA is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to other LDL-C-lowering therapies for the treatment of HeFH who have been established in pediatric patients aged 12 years and older. Use of EVOKEEZA for this indication is supported by evidence from adequate and well-controlled trials in adults with additional efficacy and safety data in pediatric patients aged 12 years and older (see Adverse Reactions [6.1] and Clinical Studies [14]).

The safety and effectiveness of EVOKEEZA have not been established in pediatric patients with HeFH who are younger than 12 years old.

8.4 Pediatric Use

Clinical studies of EVOKEEZA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

REGENERON

Manufactured by: Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-8707

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EWK.2012.0029
The app is a great innovation. Almost every need can be met by one, every curiosity satisfied. Nobody likes to pay for parking, but if you have to, the parking apps are a huge improvement over stuffing the meter with coins. Apps for large medical meetings have become indispensable. You can set your own schedule. Often the speaker’s slides are right there, embedded in the app. Birders now have every birdsong literally right at their fingertips. It is hard to imagine, but there was a time when people would wait for the evening news or even the morning newspaper to find out what is going on. Now we just instantly open a news app or get pinged with notifications.

Many of the apps we use are merely for amusement. The utility of the ones that are useful often lies in the convenience they provide — not having to do something. An app and the device that it resides on mean not having to lug around a book, take notes and watch TV to get a weather forecast.

Digital therapeutics, the subject of our cover story, are different. They have been developed to treat or manage a disease, so it’s serious business, not just fun and convenience. Our story covers several digital therapeutics that rely on cognitive behavioral techniques to change counterproductive thinking and behavior. And we zero in on the ones that have gotten approval from the FDA as prescription devices. There isn’t a separate approval pathway for digital therapeutics — yet. For the companies making these products, one of the biggest challenges is getting insurers and PBMs to cover them. Prime Therapeutics and Pear Therapeutics have entered into a value-based agreement, an indication perhaps that the data that digital therapeutics can yield will make valued-based agreements a sweet spot for them.

The coverage issues may be something of an obstacle course. But digital therapeutics have great potential for changing how disease is treated and managed in the 21st century. In the long run, there’s no holding them back.

Mike Hennessy Jr.
President and CEO of MJH Life Sciences™
Mission
Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights and strategies to pursue value-driven solutions.
DRUGS IN THE PIPELINE
18 NSCLC therapy is increasingly targeted

ONCOLOGY
20 Is cancer screening getting back to normal?

INDUSTRY ANALYSIS
31 Health insurance markets are concentrated — and getting more so
36 Much of rural America is a healthcare desert. Will the Dollar General stores be an oasis?

POPULATION HEALTH
50 Oral and dental health is crucial. But access to coverage is spotty.

DEPARTMENTS
4 Editorial Advisory Board
12 In Brief

CONFERENCE COVERAGE
53 Asembia’s 2021 Specialty Pharmacy Summit
NOW APPROVED
For your non-immunocompromised members with uncontrolled mild to moderate atopic dermatitis (AD) 12 years of age and older¹

Opzelura™ (ruxolitinib) cream 1.5%

THE ONLY FDA-APPROVED JAK INHIBITOR IN A CREAM FORMULATION¹

IN THE TRuE-AD1 AND TRuE-AD2 CLINICAL TRIALS, PATIENTS RECEIVING OPZELURA™ DEMONSTRATED MEANINGFUL RESULTS FOR¹²

SKIN CLEARANCE
As measured by Investigator’s Global Assessment–Treatment Success (IGA-TS [primary endpoint])

ITCH REDUCTION
As measured by ≥4-point improvement in Itch Numeric Rating Scale (Itch-NRS 4)

SAFETY AND TOLERABILITY
The most common adverse reactions, occurring in ≥1% of patients treated with OPZELURA™, were nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea

OPZELURA™ was studied in 2 identically designed, phase 3, double-blind, randomized, 8-week, VC trials (TRuE-AD1 and TRuE-AD2). The clinical trials included 1,249 adolescent and adult patients with AD 12 years of age and older (631 randomized in TRuE-AD1 [vehicle, n=126; OPZELURA™ 1.5%, n=253] and 618 randomized in TRuE-AD2 [vehicle, n=118; OPZELURA™ 1.5%, n=228]). At baseline, patients had an affected BSA of 3% to 20% and an IGA score of 2 or 3 on a 0- to 4-point severity scale. The primary endpoint was IGA-TS, defined as an IGA score of 0 or 1 with ≥2-grade improvement from baseline, and Itch-NRS 4 was a key secondary endpoint. The Itch-NRS 4 analysis included patients with an Itch-NRS score ≥4 at baseline (TRuE-AD1 [vehicle, n=78; OPZELURA™ 1.5%, n=161]; TRuE-AD2 [vehicle, n=80; OPZELURA™ 1.5%, n=146]).¹²
IN THE TRuE-AD1 AND TRuE-AD2 CLINICAL TRIALS, PATIENTS RECEIVING OPZELURA™ DEMONSTRATED MEANINGFUL RESULTS FOR 1,2 NOW APPROVED FOR YOUR NON-IMMUNOCOMPROMISED MEMBERS WITH UNCONTROLLED MILD TO MODERATE ATOPIC DERMATITIS (AD) 12 YEARS OF AGE AND OLDER

THE ONLY FDA-APPROVED JAK INHIBITOR IN A CREAM FORMULATION 1

OPZELURA™ was studied in 2 identically designed, phase 3, double-blind, randomized, 8-week, VC trials (TRuE-AD1 and TRuE-AD2). The clinical trials included 1,249 adolescent and adult patients with AD 12 years of age and older (631 randomized in TRuE-AD1 [vehicle, n=126; OPZELURA™ 1.5%, n=253] and 618 randomized in TRuE-AD2 [vehicle, n=118; OPZELURA™ 1.5%, n=228]). At baseline, patients had an affected BSA of 3% to 20% and an IGA score of 2 or 3 on a 0- to 4-point severity scale. The primary endpoint was IGA-TS, defined as an IGA score of 0 or 1 with ≥2-grade improvement from baseline, and Itch-NRS 4 was a key secondary endpoint.

The Itch-NRS 4 analysis included patients with an Itch-NRS score ≥4 at baseline (TRuE-AD1 [vehicle, n=78; OPZELURA™ 1.5%, n=161]; TRuE-AD2 [vehicle, n=80; OPZELURA™ 1.5%, n=146]). 1,2

OPZELURA™ CAN BE APPLIED TO AFFECTED SKIN, UP TO 20% BSA, INCLUDING SENSITIVE SKIN AREAS 1*

Learn more about the clinical studies for OPZELURA™ at OPZELURAhcp.com.

INDICATION
OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:
Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION
SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

• Active tuberculosis, which may present with pulmonary or extrapulmonary disease.
• Invasive fungal infections, including candidiasis and pneumocystosis.
• Bacterial, viral, and other infections due to opportunistic pathogens.

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

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

BSA, body surface area; FDA, Food and Drug Administration; IGA, Investigator’s Global Assessment; IGA-TS, Investigator’s Global Assessment–Treatment Success; Itch-NRS, Itch Numeric Rating Scale; Itch-NRS 4, 24-point improvement from baseline in Itch Numeric Rating Scale; JAK, Janus kinase; TRuE-AD, Topical Ruxolitinib Evaluation in AD; VC, vehicle-controlled.

*For topical use only. Not for ophthalmic, oral, or intravaginal use.
IMPORTANT SAFETY INFORMATION (continued)

SERIOUS INFECTIONS
No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.
THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia
Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations
Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions
The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy
There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation
Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

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

WS: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death [see Warnings and Precautions and Adverse Reactions].

Reported infections include:
- Active tuberculosis, which may present with pulmonary or extrapulmonary disease.
- Invasive fungal infections, including candidiasis and pneumocystosis.
- Bacterial, viral, and other infections due to opportunistic pathogens.

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

Thrombosis:
Instruct all patients, particularly those with a known history of cardiovascular events, to be alert for the development of signs and symptoms of cardiovascular events. Instruct patients who are current or past smokers at increased risk of thrombosis to stop smoking prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at an increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Esophagitis increased count 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (1%).

Infections: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials. Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Common adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater rate observed in OPZELURA compared to placebo were:
- Acneiform dermatitis.
- Pruritus.
- Fungal infection.
- Urticaria.

The incidence of adverse reactions was generally more severe in males than females in all age groups, and effects were generally more severe in males than females in all age groups, and effects were generally more severe in males than females in all age groups. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at an increased risk of thrombosis.

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Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.
Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

**DRUG INTERACTIONS**

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Exposure Registry:** There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

**Risk Summary:** Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rhesus monkeys resulted in less than a twofold increase in maternal plasma exposure at the maximum recommended human dose (MRHD) in the study, and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

**Data**

**Animal Data:** Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD), the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

**Lactation**

**Risk Summary:** There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

**Data:** Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

**Pediatric Use:** The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 years to 17 years of age with mild to moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

**Juvenile Animal Toxicity Data:** Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

**Geriatric Use:** Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

**PATIENT COUNSELING INFORMATION**

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

**Infections:** Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

**Malignancies and Lymphoproliferative Disorders:** Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

**Major Adverse Cardiovascular Events:** Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

**Thrombosis:** Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

**Thrombocytopenia, Anemia and Neutropenia:** Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

**Administration Instructions:** Advise patients or caregivers that OPZELURA is for topical use only [see Dosage and Administration].

Advise patients to limit treatment to 60 grams per week.

**Pregnancy:** Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 [see Use in Specific Populations].

**Lactation:** Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose [see Use in Specific Populations].

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

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U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 9079912; 9974790; 10639310; 10610530; 10758543; 10869870
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In Brief

It's steady as she goes in employer-based health insurance

The COVID-19 pandemic has disrupted healthcare and many parts of the U.S. economy, but employer-based health insurance? Largely unruffled, according to results of the Kaiser Family Foundation’s annual survey of employer health benefits.

The average annual premium for single and family coverage increased by 4% from 2020 to 2021, the same percentage increase as the year before, according to the survey. Covered workers shoulder 17% of the premium for single coverage and 28% for family coverage, similar to the worker share in 2020. The steadiness of the increase does not negate how fast premiums have risen: According to Kaiser, the average premium for family coverage has gone up 22% since 2016, twice the rate of inflation during that period.

The proportion of employers who offered coverage (59%) and the proportion of employees who enrolled in plans offered by their employers (62%) also saw little change between 2020 and 2021.

The broad outlines of the survey may suggest the gelling of a status quo for employer-based health benefits, but that does not mean there haven’t been notable shifts and adjustments. For example, the Kaiser survey found that the proportion of large firms offering biometric screening — checks of cholesterol levels, blood pressure and body mass index — is decreasing, from 50% in 2020 to 38% in 2021. Wellness programs have, not surprisingly, gone digital and remote. The survey respondents indicated that 21% of the programs added a digital offering in 2021 and 34% reported tweaking their programs to accommodate people working at home.

And, of course, telemedicine is ascendant. Nearly all (95%) of the employers with 50 or more employees offered telemedicine in 2021, which the Kaiser survey defined as telecommunications with a provider in a different location (email and web-based videos did not count). That’s up from 85% in 2020.

The survey also revealed an interesting swing to “level-funded” plans among small employers that are self-insured. As explained by the Kaiser researchers who conducted the survey, level-funded plans bundled self-funding with extensive stop-loss insurance. The companies that sell the coverage charge a monthly fee (as the Kaiser researchers point out, it resembles a premium) that includes a percentage of the expected cost of the provision of the healthcare benefits, a premium for stop-loss coverage and an administrative fee. The plan administrator, often an insurer, can consider the health status of the workforce, so level-funding can be a good deal for companies with employees who are young and, on average, healthy. But level-funding, because it is a form of self-insurance, escapes state premium taxes and state-mandated benefits. The Kaiser researchers reported that the survey showed a steep increase in the share of small firms with level-funded plans, from 13% in 2020 to 42% in 2021.

The Kaiser survey was conducted from mid-January 2021 through July. Representatives of 1,686 firms filled out the survey. Kaiser researchers reported the findings in Health Affairs in November.
Value-based care in oncology gets off to shaky start

The Oncology Care Model (OCM) was CMS’ main attempt to usher value-based care into oncology. What will come after OCM is unclear as the future of successor, Oncology Care First, is now very much in doubt. Regardless, results of a study of OCM’s first three years may give some value-based care proponents pause.

The 201 practices that volunteered to participate in the model spent $297 less per six-month episode of care than 534 practices in a comparison group, reported Nancy Keating, M.D., M.P.H., a professor of health care policy at Harvard Medical School and the lead author of the study published in *JAMA Oncology* in November. But that savings was offset by an average of $704 in extra payment to the participating practices to cover the cost of enhanced services, such as creation of care plans and around-the-clock access to clinicians. As a result, OCM wound up costing the Medicare program $315.6 million over a two-and-a-half-year period, according to calculations by Keating and her colleagues.

Others have previously reported on OCM’s less-than-stellar results; the study by Keating paints a more complete picture.

An accompanying editorial noted that new and expensive immunotherapy and targeted therapies were introduced during the period when practices were participating in OCM. Those new therapies constrained the ability of oncologists to make cost-saving substitutions and perhaps realize some of the potential of value-based care, wrote Raymond Osarogiabon, M.B.B.S., of Baptist Memorial Health Care in Memphis, Tennessee, and Samyukta Mullangi, M.D., and Deborah Schrag, M.D., M.P.H., both of Memorial Sloan Kettering Cancer Center in New York City. They noted that drug costs account for an increasingly large share of the cost of cancer and including them in value-based care arrangements is “problematic.”

OCM might be viewed as the 1.0 of value-based care for oncology, with the not-great results chalked up to the learning curve. Oncology Care First was going to be the chance to iron out some of the problems by, among other things, moving toward prospective capitated payment and gearing benchmarks to specific cancers. Officials at the Center for Medicare & Medicaid Innovation have said they now expect there to be a gap between when OCM ends in June 2022 and when a successor starts. The Biden administration CMS is putting an emphasis on equity issues, so equity is likely to be an important part of whatever comes after OCM.
Atopic dermatitis (AD), also known as atopic eczema, is a pruritic inflammatory skin disorder. It is distinguished by recurrent eczematous lesions with reddened, blistered, crusty or oozing skin; lichenification; and xerosis. Although the prevalence of AD in the United States is higher among children (approximately 11%-13%), recent estimates indicate that a considerable proportion of adults are affected (about 7%).

Clinical burden of atopic dermatitis
The clinical presentation of AD is heterogeneous. AD may follow a relapsing-remitting course with acute flares or occur as chronic persistent disease. AD can present on any area of the body but most frequently occurs on the inside of the elbows, back of the knees, top of the feet and lower legs.

The pathogenesis of AD is multifaceted, involves epidermal barrier dysfunction and immune system activation and is likely influenced by environmental factors. The strongest risk factor for AD is a family history of atopic diseases and especially of AD. AD is diagnosed based on clinical signs, historical features, morphology and the distribution of skin lesions. Currently, there are no biomarkers for AD. Pruritus is a prominent feature of AD and one that contributes to the substantial disease burden borne by patients. In one study of 380 adults with moderate to severe AD, most reported daily itching, and approximately 60% indicated that the itching was “unbearable” or “severe.”

Disease severity can be difficult to determine, because the symptoms of AD can fluctuate over time and depend upon bodily location; darker skin can suggest less severe skin involvement, and assessment tools have different severity categories. Similarly, several severity assessment tools require the subjective judgment of patients (e.g., regarding intensity of itch and sleeplessness). There are four validated tools to measure AD severity; however, two of these are most often used in clinical trials and may require too much time to be of use to healthcare providers: the Scoring Atopic Dermatitis (SCORAD) index and the Eczema Area Severity Index (EASI). The SCORAD composite score is based on the extent and severity of AD and on patient-reported symptoms (pruritus and sleep loss). EASI is used to determine the extent and severity of AD and focuses on four body regions (head and neck, the trunk, and the upper and lower extremities). The EASI rates four key clinical symptoms of AD: erythema (redness), induration/papulation (thickness), excoriation (e.g., scratching) and lichenification.

Healthcare and economic implications of AD
Comorbidities
In the United States, a significant association exists between AD and immune-mediated comorbidities (e.g., ulcerative colitis, pernicious anemia). Adults in the United States with AD also have a higher prevalence of cardiovascular (e.g., heart disease, high blood pressure), psychological (e.g., depression and anxiety) and other chronic conditions than do those without AD. Data from the 2013 U.S. National Health and Wellness Survey (NHWS) determined that adults with AD were more than two times more likely to report sleep disorders, depression and/or anxiety than matched controls without AD (P < .001 for all).

Quality of life
Itch triggers and exacerbates a host of AD symptoms, diminishing quality of life (QOL) for patients with AD. A study using a self-administered internet-based questionnaire indicated that adult patients with moderate or severe AD had significantly more trouble sleeping, longer sleep latency, more frequent sleep disturbances and an increased need for over-the-counter (OTC) sleep medications than those with mild AD (P < .001 for all). A population-based study demonstrated that AD is associated with marked QOL impairment for adults in the United States that restricts patients’ lifestyle (51.3%), leads them to avoid social interaction (39.1%) and affects their activities (43.3%).

Healthcare utilization and economic burden of AD
The costs associated with AD in the United States are approximately $7 billion per year (2020 U.S. dollars). Direct costs are approximately $1.7 billion, and indirect costs have been estimated at $1.04 billion. Intangible costs, estimated by patient willingness to pay for symptom relief, are approximately $4.37 billion.

Adults with AD have increased healthcare resource use compared with those without AD, and higher disease severity is associated with greater utilization. An analysis
of healthcare claims data from three different populations (commercial, Medicare and Medi-Cal) determined that, each year, adults with AD have average numbers of emergency department visits, outpatient visits and pharmacy prescriptions that are significantly greater than those for adults without AD ($P < .05$ for all). These results are consistent with an analysis of data from the 2013 NHHS, which demonstrated that adults with AD have average numbers of provider visits ($P < .001$), emergency department visits ($P < .001$) and hospitalizations ($P = .004$) that are higher than those of matched controls.23

**Guidelines for the management of AD**

Goals in the management of AD include improving skin, minimizing flares and reducing comorbidities and symptom burden (i.e., sleep disorders and itching).24 Interventions aimed at avoiding triggers, improving the skin barrier and reducing inflammation are central to meeting these goals.2

As mentioned previously, symptom severity and response to treatment can be measured using validated tools such as the EASI. The validated Investigator Global Assessment for AD (vIGA-AD), frequently used in clinical trials, is another tool to measure treatment efficacy. The vIGA-AD scale is used to measure improvement in clinical signs and has distinct categories (erythema, induration/papulation, lichenification, and oozing and/or crusting) to assess disease severity in AD.24

Guidelines for AD suggest a multifaceted approach. Basic nonpharmacologic measures (e.g., bathing, moisturizing and avoiding triggers) are recommended across all severities of AD. Pharmacologic treatment follows a stepwise progression based on disease severity.24

**Nonpharmacologic therapy**

Moisturizers are essential in AD to lubricate and soften the skin, reduce water evaporation, and attract and hold water.24 They can decrease the signs and symptoms of AD and reduce inflammation and severity.24 Severe flares or persistent disease may require wet-wrap therapy, whereby a wetted first layer of tubular bandages or gauze is applied over a topical agent, and a dry second layer is used as the outer barrier.24

**Pharmacologic**

Step-therapy recommendations for AD suggest topical therapies (e.g., topical corticosteroid) when proper skin care and moisturizers no longer suffice for lesion control.24 Topical agents are used to provide symptom management in acute flares and as maintenance therapy in moderate to severe AD. The potency and dose of TCS can be increased based on symptom severity.2 However, long-term daily use of TCSs is not recommended, because it can be associated with systemic adverse effects (e.g., hypothalamic-pituitary-adrenal axis suppression), skin atrophy, telangiectasia, striae, worsening acne and tachyphylaxis. Some of these adverse effects may persist for several months following discontinuation of TCS.24,25 Topical calcineurin inhibitors (TCIs) (e.g., Elidel, or pimecrolimus cream 1%; or Protopic, or tacrolimus ointment 0.03%, 0.1%) represent a steroid-sparing class of anti-inflammatory agents that can be used for flares or maintenance in moderate to severe AD.2 They are recommended for patients who have not responded to other topical therapies or for whom other topical therapies are not appropriate.24 However, they are generally less effective than midpotency TCSs, their prescription labeling carries a boxed warning about the risk of malignancy and burning or itching may be experienced during early use.24,25 Eucrisa, or crisaborole ointment 2%, a nonsteroidal anti-inflammatory PDE4 inhibitor, has a favorable safety profile but limited efficacy in patients with mild to moderate disease.24

Some patients with an insufficient response to topical therapy or severe disease may require phototherapy or treatment with systemic corticosteroids or other systemic immunosuppressants such as cyclosporine A, methotrexate, azathioprine or mycophenolate mofetil.2 Dupixent (dupilumab), a human monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling, is FDA approved for the treatment of patients 6 years and older with moderate to severe AD not adequately controlled with topical prescription therapies or for whom those therapies are not advisable.26 Although Dupixent demonstrates good efficacy, has a favorable safety profile and requires no clinical laboratory monitoring, it takes time to start working, and the subcutaneous route of administration may limit its use.24,25,26 Despite the availability of numerous therapeutic options, there remains an unmet need for additional safe and effective medications for patients with AD.

**Formulary decision-making and payer considerations**

The results of a study using 2015 data from the Truven Health Analytics MarketScan Commercial and Medicare Supplemental databases revealed that utilization of TCSs or TCIs for AD affects pharmacy budget, irrespective of treatment choice.29 There were marked differences in annual prescription costs per patient based on the mechanism of action (TCI versus TCS) and TCS strength.29 With the avail-
ability of new agents in recent years and novel therapies under development, formulary decisions in AD will become more complex.

**Barriers to appropriate therapy**
Barriers to safe and effective AD therapy remain high. Access to certain agents is limited, and payers have requirements for changing therapy.

**Access and payer requirements**
Access to new medications can be a challenge for healthcare providers, and it may depend on the patient’s insurer and prescription drug coverage. Additionally, payers may restrict prescriptions for newer agents, such as biologics and small molecules (e.g., Janus kinase, or JAK, inhibitors), to specialists such as dermatologists or allergists, because their use may require a knowledge base greater than primary care physicians can offer.

Lack of healthcare insurance may also limit a patient’s access to specialists and the newer therapies they may prescribe. Moreover, the cost of newer agents or out-of-pocket costs may limit patient access to the most beneficial therapy.

Step therapy may require physicians to try several regimens before they find one that adequately controls disease. This can result in a significant time delay for relief of AD symptoms. For example, payers often require a 30-day trial of topical TCS or TCI therapy before other therapies are considered. Payer step-therapy requirements can also restrict access of certain agents, causing a roadblock to the most safe and effective AD therapy for a particular patient.

**Cost**
The affordability of TCSs prompts the off-label prescribing of these agents. However, medium- to high-potency TCSs are not intended for daily, long-term use. At the same time, lack of insurance coverage and the cost of TCIs and Dupixent may restrict their use. Less expensive options on formulary may not be as effective as newer, albeit costlier, therapeutics. The high cost of newer therapies may also limit a patient’s access to specialists and the newer therapies they may prescribe. More importantly, the cost of newer agents or out-of-pocket costs may limit patient access to the most beneficial therapy.

Balancing safety and efficacy
Systemic therapy may be necessary for severe disease, especially when it negatively impacts QOL. Older systemic medications are immunosuppressants and nonspecific. They require a high level of monitoring, including blood tests, and carry the risks related to systemic immunosuppression. They are not the best options for long-term treatment.

**Evolution to targeted therapy**
The landscape in AD therapies is changing. Targeted agents offer improved safety and efficacy profiles and can modify the disease course, quickly resolve symptoms and enable patients to enter a maintenance phase. Importantly, new therapies in development for AD address some of the most important symptoms that impact QOL (i.e., itch and sleep disturbances). Emerging systemic therapies for AD include biologics and oral JAK inhibitors. Promising new topical agents such as JAK inhibitors, which inhibit key regulators of pro-inflammatory signals, are in clinical development.

**Clinical development of novel targeted agents: JAK pathway**

**JAK inhibition for AD**
The JAK family includes JAK1, JAK2, JAK3 and tyrosine kinase 2. The JAK-STAT pathway regulates the differentiation of T helper 2 cells. In addition, several cytokines thought to play a role in the pathogenesis of AD (e.g., IL-4, IL-31) utilize the JAK-STAT pathway of signal transduction. The hyperimmune response in AD, specifically the upregulation of IL-4, plays a key role in skin barrier dysfunction. IL-31 is also implicated in the development of AD, as increased production is associated with nerve crosstalk (i.e., the itching sensation) and worsening pruritus.

JAK inhibitors represent a new direction in the treatment of AD. JAK inhibition targets the itch-scratch cycle by quelling sensory neurons and improving the skin barrier by reducing inflammation. The inhibitors selectively bind to different JAK proteins.

Oral JAK inhibitors under investigation for AD include Olumiant (baricitinib, which binds to JAK1/2) and Rinvoq (upadacitinib) and abrocitinib (which binds to JAK1). Concerns about the safety of oral JAK inhibitors approved for other indications (Xeljanz, tofacitinib; Olumiant; Rinvoq) because of adverse effects such as serious infections, blood vessel disorders and malignancies have resulted in the FDA extending the review period for an AD indication. Of note, the prescribing information for Xeljanz, Olumiant and Rinvoq include boxed warnings regarding serious infections, malignancy and thrombosis; the boxed warning for Xeljanz also includes risk of mortality.

In September 2021, the FDA approved Opzelura (ruxolitinib cream 1.5%) for the short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised patients 12 years of age and older with disease not adequately controlled with topical prescription therapies or when those therapies are not advisable. This is the first topical JAK inhibitor approved for this indica-
tion. Although the prescribing information for Opzelura carries the same boxed warning as that for oral JAK inhibitors, in the TRuE AD1 and TRuE AD2 clinical trials that supported the FDA approval, there were no safety signals attributable to systemic JAK inhibition. Safety concerns for this topical agent are not likely to be as great as those for oral JAK inhibitors.

**Ruxolitinib**

Ruxolitinib cream has a dual mode of action that targets the pruritic and inflammatory effects of AD with direct delivery to the skin. The efficacy and safety of ruxolitinib cream in patients at least 12 years old with mild to moderate AD were assessed in the two large, double-blind, vehicle-controlled phase 3 TRuE AD1 and TRuE AD2 trials. Patients were required to have AD for at least two years, an Investigator’s Global Assessment (IGA) score of 2 or 3, and 3% to 20% of their body surface area affected. A total of 1,249 patients were randomized (2:2:1) to receive 0.75% ruxolitinib, 1.5% ruxolitinib or vehicle cream twice daily for eight weeks. The primary end point for both studies was the percentage of patients achieving IGA treatment success, defined as clear or almost clear skin with at least a two-grade improvement from baseline at week eight. Significantly more patients given ruxolitinib in TRuE AD1 and TRuE AD2 (0.75% ruxolitinib, 50.0% and 39.0%, respectively; and 1.5% ruxolitinib, 53.8% and 51.3%) met the primary end point versus those given vehicle (15.1% and 7.6%, respectively) (P < .0001 for all). Ruxolitinib 1.5% cream was associated with a significant reduction in itch by 12 hours, with even greater reductions reported over eight weeks. Ruxolitinib cream also had a favorable safety profile. The percentage of adverse effects was similar across treatment groups and among both studies. The most common treatment-related adverse effect was application-site burning, which occurred at the highest frequency in the vehicle group. There were no safety signals attributable to systemic JAK inhibition. The long-term safety of ruxolitinib is currently being evaluated in 44-week extension periods for both studies.

In August, the Institute for Clinical and Economic Review issued its final policy recommendations regarding the effectiveness and value of JAK inhibitors and monoclonal antibodies for the treatment of AD. The New England Comparative Effectiveness Public Advisory Council voted 12-1 in favor of ruxolitinib cream for mild to moderate AD compared with topical emollients alone.

**Other JAK inhibitors in development**

**Delgocitinib**

Delgocitinib, a pan-JAK inhibitor (JAK1/2/3, TYK2), is approved in Japan as an ointment for AD. Two phase 3 trials, DELTA 1 and DELTA 2, are currently enrolling patients with moderate to severe chronic hand eczema.

**ATI-1777**

The efficacy, safety, tolerability and pharmacokinetics of topical ATI-1777, a JAK1/3 inhibitor, were investigated in a phase 2a, multicenter, randomized, double-blind, vehicle-controlled trial of 50 patients with moderate to severe AD. The primary efficacy end point was the percent change from baseline in the modified EASI (mEASI) score, which excludes body surfaces not treated in the trial, at week 4. ATI-1777 was associated with a 74% reduction in mEASI score compared with vehicle (41%) (P < .001). ATI-1777 had a favorable safety profile. The incidence of adverse effects was similar between the two groups. The most common adverse effects in the ATI-1777 group were increased blood creatinine phosphokinase and headache. There were no cases of thrombosis.

**Conclusions**

AD is associated with considerable clinical and economic burdens. Itching and sleep disturbances are two of the most troubling symptoms that occur with AD, and they have a substantial impact on patients’ QOL. JAK inhibitors represent a new direction in AD therapy. Their mechanism of action directly targets the pruritic and inflammatory effects of AD. Topical JAK inhibitors, such as ruxolitinib cream, may offer these benefits without the systemic effects associated with oral JAK inhibitors.

References are available at ManagedHealthcareExecutive.com.
NSCLC therapy is increasingly targeted

Targeted therapies that zero in on cancer with particular genetic anomalies are playing an increasingly important role in the treatment of lung cancers as researchers gain a clearer understanding about the specific "driver mutations" involved in cancer cell growth, down to the level of mutations in certain genes.

This kind of mutation-specific targeted therapy has come on especially strong as a strategy for treating patients with non-small cell lung cancer (NSCLC), which accounts for between 80% and 85% of lung cancer cases. The incidence of lung cancer in the United States has been declining, but lung cancer is still the leading cause of cancer death in the country, accounting for about 25% of cancer deaths each year.

Targeted therapies are the cornerstone of this kind of precision medicine. They can be either small molecules or monoclonal antibodies. When the FDA approves a targeted therapy, it typically approves a companion diagnostic test that identifies the biomarkers that determine whether the targeted therapy is appropriate.

Researchers have determined several genes play a key role in lung cancer, including EGFR, KRAS, MET, LKB1, BRAF, PIK3CA, ALK, RET and ROS1. Research of therapies that target the mutations of these genes has expanded over the past decade, leading to the approval of several important therapies targeting EGFR, KRAS and MET mutations.

The KRAS gene has been particularly challenging to develop a therapy against. The KRAS protein doesn’t have “deep pockets” for drugs to bind to, making it difficult to block activated KRAS. But investigators have begun exploiting a specific point on the gene, KRAS G12C.

A therapy approved in May 2021 forms an irreversible bond with cysteine residue of KRAS G12C, holding the protein in its inactive form. The therapy, Amgen’s Lumakras (sotorasib), was granted accelerated approval from the FDA, making it the very first therapy to address a KRAS mutation in any cancer. Lumakras is used to treat adult patients with NSCLC whose tumors have a KRAS G12C mutation and who have received at least one prior therapy. KRAS mutations are present in about 13% of NSCLC cases. Regulators also approved two companion diagnostics: QIAGEN therascreen KRAS RGQ PCR kit and the Guardant360 CDx.

Research continues on Lumakras. A trial assessing Lumakras alone and in combination continues. A phase 2 trial of the drug as a first-line treatment for NSCLC was scheduled to start last month. Lumakras is also being studied as a treatment for other diseases, such as moderate-to-severe liver impairment.

KRAS G12C is the target of another NSCLC therapy in development, Mirati Therapeutics’ adagrasib. The company announced in June 2021 that adagrasib has received breakthrough therapy designation for this indication. Data were presented at the European Lung Cancer Virtual Congress in March 2021 from an early-stage trial that showed 45% of the 51 patients evaluable had a partial response to treatment with adagrasib.

A couple of leading therapies are designed to home in on EGFR and MET receptors. In May 2021, the FDA approved Rybrevant (amivantamab-vmijw), a bispecific antibody directed against EGFR and MET receptors. Developed by Janssen,
the drug is used to treat adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutation who have progressed with chemotherapy. Rybrevant, administered intravenously, had previously received the FDA's priority review and breakthrough therapy designation.

At the same time, the FDA approved Guardant Health's Guardant360 CDx liquid biopsy as a companion diagnostic. The test will be used for tumor mutation profiling to identify patients with locally advanced or metastatic NSCLC who harbor the EGFR exon 20 insertion.

A first
Rybrevant is the first drug the FDA has approved for patients with NSCLC who have the EGFR exon 20 mutation. About 2% to 3% of patients with NSCLC have these mutations, and they are the third most common type of EGFR mutation. Patients with this mutation have a worse prognosis because it causes rapid cell growth and spread of cancer. Five other targeted therapies to treat EGFR mutations in NSCLC are available, but they target EGFR genes that have exon 19 deletion and exon 21 substitution mutations. Janssen is also testing Rybrevant as a treatment for patients with those mutations. At the 2021 annual meeting of the American Society of Clinical Oncology, the company released data about a phase 1 trial of Rybrevant in combination with lazertinib, an experimental therapy that Janssen licensed from Yuhan Corp., a South Korean company.

The combination led to a median duration of response of 9.6 months. Janssen licensed from Yuhan Corp., a South Korean company.

Targeting MET
Over the past year, two therapies targeting a different mutation, the MET exon 14 skipping alteration, have been approved, providing the first options for this mutation. The MET gene encodes for a tyrosine kinase receptor that activates signaling pathways involved in cell proliferation, survival and growth. The MET exon 14 skipping alteration is seen in about 3% to 4% of cases of NSCLC. Patients with MET exon 14 skipping NSCLC are most likely to have a smoking history.

In February 2021, the FDA approved EMD Serono's Tepmetko (tepotinib) for the treatment of adult patients with metastatic NSCLC with MET exon 14 skipping alterations. Tepmetko is a once-daily oral therapy administered as two 225-milligram tablets (450 milligrams in total) and is the first oral MET inhibitor approved as a treatment for NSCLC.

Applications for Tepmetko have been submitted to other regulatory agencies, including the European Medicines Agency and in Australia, Switzerland and Canada under the FDA's Project Orbis initiative, which provides a framework for concurrent submission and review of oncology medicines among international partners.

In another analysis, Tepmetko demonstrated efficacy in patients with MET exon 14 skipping NSCLC with brain metastases. Brain metastases are reported in 20% to 40% of these patients and are associated with poor prognosis.

A third analysis from this study was with a cohort of patients with NSCLC with MET amplification. In this group, Tepmetko showed potential, especially in patients who had not been previously treated.

Novartis' Tabrecta (capmatinib) is another MET inhibitor therapy. It was approved in May 2020 for patients whose tumors have a mutation that leads to MET exon 14 skipping. Tabrecta is given twice daily as 400-milligram oral medication. Foundation Medicine’s FoundationOne CDx has been approved as a companion diagnostic.
During the pandemic, screenings fell significantly for just about all types of cancer as COVID-19 cases surged. RAND documented the dip in a study using a database that includes 6.8 million people covered by employer-sponsored research. Between March and June of 2018, 60,344 people were screened and 2,961 cancers detected. During that same period in 2020, 15,453 patients were screened and 1,985 cancers were detected.

According to the American Cancer Society (ACS), healthcare staff and resources were reallocated to address the priority needs of the pandemic. Additionally, patients were afraid to visit the doctor or go into a treatment center, worrying that they might contract COVID-19 — especially patients who were immunocompromised. Many patients postponed routine wellness exams, an ideal opportunity to discuss and address cancer screenings. ACS also found that financial and job insecurity during the pandemic factored into the decline in screenings.

Richard R. Barakat, M.D., physician-in-chief and director of the Northwell Health Cancer Institute in New York, says the National Cancer Institute modeling branch predicts a 1% increase in deaths through 2030 and 10,000 additional deaths due to breast and colon cancer because of the decrease in screenings.

Uneven rebound
As people began getting vaccinated, the numbers of those getting cancer screenings in 2021 increased significantly, although not always to pre-pandemic levels. Barakat says screening rates were mostly back to normal this fall as the number of people vaccinated against increased and infection rates decreased. “Most (screenings) have returned to normal, but colonoscopy lags behind perhaps because it’s an invasive procedure,” he says. Barakat also says it is worrisome that the rebound in mammography rates among Black and Latino women is lagging behind the rate for White women, a gap that may accentuate existing racial disparities in cancer screening.

When Cardinal Health Specialty Solutions surveyed oncologists in early 2020, the responses indicated that cancer screening had decreased by 90%, according to Bruce Feinberg, D.O., its chief medical officer. A survey this summer found that 70% of oncologists reported that patients were still postponing screening.

Cheryl Stanski, M.D., FACS, chief medical director of outreach for Holston Medical Group, a 230-provider group in Kingsport, Tennessee, believes things are slowly returning to normal. “Patients understand that we’re in a ‘new normal’ and health care must continue,” she says. “We aren’t at pre-pandemic levels, but we’re looking at surpassing the number of patients screened and diagnosed compared to 2020, which is hopeful. I believe people have accepted that COVID-19 is not going away and it’s important to ensure we continue our health journey, and lives overall, in the best way possible.”

Stanski says the screening numbers are lower than they were before the pandemic but are edging closer. The shutdowns and general retreat from healthcare during the first few months of the pandemic created a backlog of screenings that Holston and other providers are working through, she says. But many people are still reluctant to get in-person care. Stanski says the group has sought out patients who are already experiencing potential symptoms of cancer to prioritize screenings and diagnosis as early as possible.

By strategically reaching out to those patients, our 2021 diagnoses (326 breast cancer diagnoses and 112 colon cancer diagnoses) were higher than we would have expected.”

Continued on page 30
The first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic

The treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate

The treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor 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.

Visit LIBTAYOhcp.com for more information
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO 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 immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated endocrinopathies: For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Immune-mediated endocrinopathies: (cont’d)

- **Hypophysitis:** LIBTAYO 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. Withhold or permanently discontinue LIBTAYO depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

- **Thyroid disorders:** LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity.

- **Thyroiditis:** Thyroiditis occurred in 0.5% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

- **Hypothyroidism:** Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hypothyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hypothyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

- **Diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis: Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/26) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

**Immune-mediated nephritis with renal dysfunction:** LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated dermatologic adverse reactions:** LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Other immune-mediated adverse reactions:** The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

- **Cardiac/vascular:** Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis.

- **Nervous system:** Menigitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Other immune-mediated adverse reactions: (cont’d)

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroid to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Complications of allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. 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.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities (≥2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

Use in Specific Populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see Brief Summary of Prescribing Information on the following pages.

ALK, anaplastic lymphoma kinase, EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.


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LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Cutaneous Squamous Cell Carcinoma

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

1.2 Basal Cell Carcinoma

LIBTAYO is indicated for the treatment of patients:
- with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

1.3 Non-Small Cell Lung Cancer

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥ 50%) as determined by an FDA-approved test [see Dosage and Administration (2.1) in the full prescribing information], with no EGFR, ALK or ROS1 aberrations, and is:
- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-1 ligand 1 (PD-L1) blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest 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. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor 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.

Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. In general, if LIBTAYO 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 immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld for pneumonitis, 9 reinitated LIBTAYO after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis.

Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients.

Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld for colitis, 4 reinitated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis.

Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reinitated LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withdraw LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 4 (0.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Hypophysitis

LIBTAYO 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. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue...
LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

Hyperthyroidism: Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 83% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reintiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

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 LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reintiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reintiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemolytic urine reticulocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

5.3 Complications of Allogeneic HSCT

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacutue graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic vein-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. 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.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. 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. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 152 patients with advanced BCC (Study 1620), 355 patients with NSCLC...
The safety population characteristics were: median age of 68 years (38 to 110 weeks). The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%). Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepis, and pneumonia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, pruritis, and confusion state. The most common (≥ 20%) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions (≥ 2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepis, skin infection, and hypercalcemia. The most common (≥ 4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hypophosphatemia.

Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

### Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>N=219</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General and Administrative Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashb</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Pruritusd</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrheaa</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal paina</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

(continued)
Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03. Percentages are based on the number of patients with at least 1 post-baseline value ≥ 1% of patients receiving LIBTAYO.

Table 4 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 5 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

### Table 4: Adverse Reactions in ≥ 10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N = 132</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.

- a. Composite term includes fatigue, asthenia, and malaise
- b. Composite term includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain
- c. Composite term includes rash maculo-papular, rash, dermatitis, dermatitis acneform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematous, and urticaria
- d. Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection
- e. Composite term includes dyspnea and dyspnea exertional
- f. Composite term includes hypertension and hypertensive crisis

### Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time prolonged</td>
<td>2.3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Toxicity was graded per NCI CTCAE v. 3.03.

- a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

Non-Small Cell Lung Cancer (NSCLC)

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Studies (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥ 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

### Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Decreased appetite</td>
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<td>0.6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.

- a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness
- b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, and skin reaction
- c. Fatigue is a composite term that includes fatigue, asthenia, and malaise
- d. Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paracancerous pneumonia, pneumonia, pneumonia bacterial, and pneumonia klebsiella
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 LIBTAYO 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 LIBTAYO 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 these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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LIB.21.02.0054 02/21
Continued from page 20
diagnoses) are close to surpassing our 2020 numbers and give us hope we’re returning to normal screening rates,” Stanski says.

Prior to the pandemic, many community-based cancer programs in the Karmanos Cancer Network in Detroit sponsored screening events, which typically attracted those without primary care providers to schedule screenings, as well as the underinsured. “Unfortunately, like most providers across the country, after the onset of the pandemic we had to make the decision to cancel all community cancer screening events, and that continued for seven months,” says Lauren Lawrence, vice president of the network.

In June 2020, after the initial surge in Michigan, the ACS assembled a Cancer Screening Task Force, which included healthcare leaders from across the state. The task force developed a campaign to educate the public that it was safe to come back to healthcare facilities for screenings by promoting the message “Cancer does not wait for COVID,” Lawrence said relatively small numbers of people have taken advantage of prostate and breast screening events in rural Michigan. “Despite the minimal turnout, it was a sign people were beginning to respond to our cancer screening campaigns and focus on their personal healthcare needs.”

In March 2021, Karmanos held three colorectal screening events and one prostate screening event in that same rural region emphasizing screening protocols and distancing requirements. “We had more than 500 participants this time,” Lawrence says. “Cancer screenings are trending upward but are not back to pre-COVID levels and we continue to experience dips when we encounter surges in COVID volumes.”

Michael Zinner, M.D., CEO and executive medical director of the Miami Cancer Institute at Baptist Health South Florida, says the number of people getting screened for cancer has increased. He is worried, though, that “we won’t be able to catch up fast enough.” Zinner says a large part of the patient population is still hesitant about getting screened. That hesitancy is part of an overall reluctance to return to physicians for routine care.

Long-term consequences

There are overdiagnosis and overtreatment in cancer, so the dip in screening may have spared some people tests and treatment that aren’t necessary and even harmful. On the other hand, oncologists are bracing for a pandemic cohort of patients with later-stage cancers who will have presumably worse outcomes than if they had been screened and their cancers perhaps diagnosed at an earlier, more treatable stage. The decrease in screenings over the past 18 months, in Stanski’s experience, has already resulted in some cancers being diagnosed at a later stage. She says one of her patients with breast cancer noticed a lump in early 2020 when the pandemic began but did not seek care until this year. “Because of the delay in diagnosis and treatment, the cancer is much larger and has spread,” she says. “It has become more difficult to treat and may be impossible to cure. With later diagnoses, patients need more aggressive treatments. These often have heavier costs, compared with preventive procedures, as well as more severe health complications and risk of loss of life.”

“Screenings allow a medical provider to identify cancer in its early stages,” says Timothy Quinn, M.D., a high-profile family physician in the Jackson, Mississippi, area who is interviewed often on local news programs and serves on city health organizations. Although the Delta variant caused patients to delay their wellness exams again, Quinn says patients are rescheduling and coming back into the office for their visits, including screenings, at a greater rate. “As COVID-19 infection rates decline, we can anticipate that wellness visits will increase,” he says. “COVID-19 has been unpredictable; however, with the recent advancements and updates in boosters and potential treatments, patients seem more confident to get their wellness back on track.”

Keith Loria is a freelance writer in the Washington, D.C., area.
Industry Analysis

Health insurance markets are concentrated — and getting more so

At the state and local levels, an increasing number of markets are dominated by one or a handful of insurers. Experts say it is part of a vicious cycle of payers responding to provider consolidation and vice versa. by JOSEPH BURNS

Just as employees are reviewing health insurance options offered by employers and only weeks before individuals and families can enroll in coverage through the Affordable Care Act’s marketplaces, the American Medical Association (AMA) reports that most health insurance markets in the United States have become even more concentrated than they were last year.

Over the past 20 years, most health insurance markets have become less competitive, limiting consumers’ options based on an analysis of market concentration for 384 metropolitan statistical areas (MSAs), the 50 states and the District of Columbia, the AMA researchers showed.

The health insurance market is not consolidated at the national level. But 14 states and almost half (46%) of the MSAs had one insurer with 50% or more of the commercial health insurance market, the report said. The AMA researchers found that almost three-quarters (73%) of the MSAs were considered highly concentrated according to standard definition of market concentration, an increase from 71% in 2014.

The market concentration has not gone unnoticed. Congress passed and former President Donald Trump signed into law the Competitive Health Insurance Reform Act (CHIRA) of 2020. Trump administration Justice Department officials said CHIRA would bolster antitrust enforcement efforts. Traditionally, the Justice Department has reviewed health insurance mergers and the Federal Trade Commission, mergers of hospitals, doctors and pharmaceutical companies.

The McCarran-Ferguson Act delegates regulation of insurance to the states. Martin S. Gaynor, an economist at Carnegie Mellon University in Pittsburgh and an expert on competition and antitrust issues, says CHIRA underscored that the McCarran-Ferguson Act does not shield health insurers from antitrust laws. But in Gaynor’s view, that was commonly understood about McCarran-Ferguson, and he points to the antitrust actions the Justice Department took to block Anthem’s proposed acquisition of Cigna and Aetna’s plan to acquire Humana. Both deals fell apart in 2017. “I don’t think (CHIRA) does much. But it’s a good thing to have this made explicit in legislation,” Gaynor says. Other legal experts do not think it was quite so clear that McCarran-Ferguson allowed for federal antitrust intervention in health insurance markets.

In any event, until the Justice Department — or an aggrieved hospital, health system or other insurer — brings a case under CHIRA, the effect of the law will remain untested. There are other ways the Biden administration could tackle market concentration, notes Sabrina Corlette, a research professor and co-director of the Center on Health Insurance Reforms at Georgetown University’s McCourt School of Public Policy in Washington, D.C. It could move to prohibit anti-competitive contractual clauses or require insurers (or health systems) that merge to put temporary limits on price increases after a merger, Corlette notes.

Discussion of health insurance concentration require a similar

Continued on page 35

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

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EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON
• **Powerful efficacy** and **robust anatomic outcomes** across all indications as shown in 8 phase 3 clinical trials\(^1\)–\(^8\)
• A broad range of indications and **dosing flexibility** across several FDA-approved indications\(^1\)

• **Demonstrated safety** profile across 4 VEGF-driven retinal diseases: Wet AMD, DR, DME, and MEIRVO\(^1\)
• As of March 31, 2020, postmarketing reports in the global safety database of IOI or retinal vasculitis have accounted for 1 out of every 6 million injections (0.00002%), and all such cases were associated with endophthalmitis

• 9 years of extensive real-world experience\(^1\) and ~13 million doses administered to >1 million eyes since launch (and counting)\(^9\)
• Established and consistent **dosing options**
• Stable pricing since launch in 2011

DME = diabetic macular edema; DR = diabetic retinopathy; FDA = US Food and Drug Administration; IOI = intraocular occlusion; MEIRVO = macular edema following retinal vein occlusion; RAO = retinal arterial occlusion; VEGF = vascular endothelial growth factor.

**ADVERSE REACTIONS**

• Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
• The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
• Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

**INDICATIONS**

EYLEA\(^a\) (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

References:

Please see Brief Summary of full Prescribing Information on the following page.
5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 45 minutes of intravitreal injection, including with EYLEA (see Adverse Reactions (6.2)). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the position of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibition, including EYLEA. ATEs are defined as cerebrovascular, venous, or arterial ischemic events, or vascular death (including deaths of unknown cause). The incidence of ATEs following intravitreal Eylea treatment was assessed in 10 randomized, double-masked, controlled clinical studies. ATEs were observed in 1.5% of patients treated with EYLEA compared with 1.5% (6 out of 395) in patients treated with ranibizumab; through 96 weeks, the incidence was 2.6% (20 out of 770) in the control group from baseline to week 52. If ATE is defined in the combined group of patients treated with EYLEA compared with 1.5% (20 out of 218) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA from week 2 to week 52.

6 ADVERSE REACTIONS

The following serious, nonserious serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity (see Warnings and Precautions (5.1))
- Endophthalmitis and retinal detachments (see Warnings and Precautions (5.3))
- Increase in intraocular pressure (see Warnings and Precautions (5.2))
- Thromboembolic events and retinal detachments (see Warnings and Precautions (5.3))

6.1 Clinical Trials Experience

At least 1,000 patients treated with EYLEA were treated under well-controlled conditions, with adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same drug or another drug and may not represent the rates observed in clinical practice.

In a randomized, double-masked, controlled clinical study, 595 patients were treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with EYLEA compared with 2240 patients treated with ranibizumab. For these reasons, the comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

6.2 Immunogenicity

Arterial ischemic events (ATEs) following intravitreal use of EYLEA may be associated with an increase in intraocular pressure. These increases may manifest as retinal detachment or endophthalmitis or retinal detachments. Endophthalmitis and retinal detachments, including retinal tears, are described elsewhere in the labeling (see Warnings and Precautions (5.1)).

Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 below). Statements on efficacy in patients not enrolled in the trials are based on the safety data from the phase 3 VIVID and VISTA trials are not available.

Less common serious adverse reactions reported in ≥1% of the patients treated with EYLEA were hyperpigmentation, retinal detachment, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (ROD): The data described below reflect exposure to EYLEA in 194 patients with DME who were treated with the 2 mg dose, in 2 double-masked, controlled clinical studies (VIVID and VISTA) for 24 months (with active control in year 1). Safety data collected in the patients randomized to treatment with EYLEA were consistent with those reported in the PANORAMA trial.

The safety and effectiveness of EYLEA in pediatric patients have not been established. There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive performance (see Warnings and Precautions (5.1)).

8.4 Pediatric Use

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered more than once weekly during gestation for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.2-4.4% and 15-20%, respectively.

8.5 BreastfeedIng

Breastfeeding is not recommended during breastfeeding.

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Continued from page 31

examination of consolidation among hospitals, health systems and physician groups. It almost seems as if one begets the other because when insurers consolidate, hospitals and health systems at least need to consider whether they should do so as well. “Consolidation is rampant throughout the health industry on the insurance side and on the provider side,” says Corlette. “It’s kind of a vicious cycle that’s both an offensive strategy and a defensive strategy.”

Lovisa Gustafsson, MBA, vice president of controlling health care costs for The Commonwealth Fund, agrees, saying, “It’s almost like there’s a compounding effect. There is definitely some sort of a tension in a market when insurers or hospitals combine, as if maybe they egg each other on.”

But even if insurers did not consolidate, there are enough benefits for health systems to acquire hospitals and physician groups, if only to gain more geographic reach or to make themselves more attractive to employers, she adds. “Why wouldn’t health systems want more negotiating leverage to command higher prices?” Gustafsson asks. “That’s why we see that when hospitals consolidate — prices go up.” In addition, hospitals and health systems can get higher profit margins from drug companies when they acquire physician practices and administer prescription medications in the hospital or a hospital-affiliated outpatient clinic, she notes.

In theory, consolidation among insurers (and providers) could result in cost reductions because of lower overhead and administrative costs. But the consolidation brings pricing power that tends to obscure any of those efficiency gains. A Commonwealth Fund report in 2015 showed that consolidation among health insurers leads to increases in premium costs, even though insurers with larger market share generally obtain lower prices from health care providers. The Commonwealth Fund’s analysts noted that more research is needed on the effects of insurer consolidation on enrollment, premiums and the costs of health insurance.

Ideally, that research would show results for each insurer, plan, customer segment and the effects on local markets, the fund added. For example, researchers for the AMA showed that after UnitedHealth Group completed its acquisition of Sierra Health Services in 2008, health plan premiums in Nevada increased by 13.7%. “The findings suggest that the merging parties exploited the market power gained from the merger,” the AMA said.

It is difficult, however, to make blanket statements about whether a merger or acquisition among health insurers is good or bad for consumers without also considering what happens months or years after the fact, Gustafsson adds. “If there’s no competition, do you get good offerings in terms of lower prices or more consumer choice?” she asks. In some cases, premiums prices go up and in others, they go down, Gustafsson says. Because each market is different and many factors affect insurers’ ability to raise or lower premiums, it’s difficult to assess how a merger of insurers will affect consumer costs, she explains.

The research on what happens when hospitals and health systems combine is more robust. “We have more evidence and a clear-cut story there,” Gustafsson notes. “When hospitals consolidate, prices go up. We see that time and again. And when hospitals buy physician practices, prices go up.”

Joseph Burns is a Cape Cod, Massachusetts, resident and an independent journalist who covers healthcare and health insurance.
Dollar General is poised to become the latest retailer to start providing healthcare. The discount retailer has hired a chief medical officer and announced that it is considering offering a variety of services — including telehealth, eye care and prescription pickup — as it focuses on rural areas that have been called "healthcare deserts" because options are so scarce.

At this point, Dollar General is playing its healthcare cards close to its chest. The company declined to discuss its plans with Managed Healthcare Executive. But in a news release this summer, the company said it was positioning itself to be a provider in the country’s rural areas. “Our customers have told us that they would like to see increased access to affordable healthcare products and services in their communities,” CEO Todd Vasos said in the release. “Our goal is to build and enhance affordable healthcare offerings for our customers, especially in the rural communities we serve.” Dollar General, headquartered in suburban Nashville, Tennessee, has more than 17,000 stores. Even though it is a presence in rural America, the company says that 75% of the U.S. population lives within 5 miles of one of its locations.

The retailer also said it was increasing healthcare offerings such as cough and cold medications and dental products in many stores. The same announcement included the news that the company was appointing Albert Wu, M.D., to the new position of vice president and chief medical officer to develop the retailer’s healthcare services. The release said Wu, who came to Dollar General from McKinsey & Co., was tasked with “establishing and strengthening relationships with current and prospective healthcare product and service providers to build a comprehensive network of affordable services for DG (Dollar General) customers.”

Other retailers have started to provide healthcare. CVS pioneered retail healthcare with its MinuteClinics and has added HealthHUBs to provide chronic care management. Walgreens has partnered with VillageMD, and the two companies announced in mid-October that they are aiming to have 600 primary care practices operating in Walgreens stores by 2025 and 1,000 by 2027. Walmart has announced ambitious plans to provide healthcare, and it might be a competitor with Dollar General in some rural areas, although Walmart’s push into healthcare may be wavering.

In an August earnings call, Vasos talked about “healthcare deserts” and the role that his company could play in providing services in those areas. “It could be a really big deal, not only for our top line and bottom line at Dollar General, but even more so making (Dollar General stores) even more relevant to those consumers in rural America that have to drive now 30, 40 minutes for an eye exam as, an example, or even to see a doctor.”

Vasos did not offer many specifics but said Dollar General might offer services such as eye care, telemedicine and prescription pick-up. He dismissed, though, the idea of the discount chain setting up in-house pharmacies. Vasos said the retailer would develop a game plan “over the next many quarters.”

Brock Slabach, chief operations officer at the National Rural Health Association, said his group would support Dollar General offering more healthcare services.
Much of rural America is a healthcare desert.

To be successful, if Dollar General offered telehealth services, it would have to serve as a complement to local providers rather than a substitute.

—PEYIN HUNG, PH.D., AN ASSISTANT PROFESSOR AT THE ARNOLD SCHOOL OF PUBLIC HEALTH

“IT’S IMPORTANT TO EXPAND ACCESS TO CARE IN RURAL COMMUNITIES.” THE LACK OF HEALTHCARE PROVIDERS IN RURAL AMERICA IS A LONG-STANDING PROBLEM. RURAL HOSPITALS HAVE CLOSED. PHYSICIANS HAVE BEEN IN SHORT SUPPLY FOR DECADES. BUT THE PROBLEM HAS GOTTEN SOME FRESH ATTENTION, AND “UNDERSERVED” HAS BEEN REPLACED BY HEALTHCARE DESERT.

GOODRX, THE PRESCRIPTION PRICE COMPARISON WEBSITE, PUBLISHED A WHITE PAPER ON HEALTHCARE DESERTS IN SEPTEMBER. USING DATA FROM THE FEDERAL GOVERNMENT’S HEALTH RESOURCES & SERVICES ADMINISTRATION AND OTHER SOURCES AND THEIR OWN DEFINITIONS OF WHAT CONSTITUTES A DESERT (USUALLY A DRIVE OF SOME DURATION), THE COMPANY RESEARCHERS IDENTIFIED HOSPITAL, PHARMACY AND OTHER KINDS OF HEALTHCARE DESERTS. FOR EXAMPLE, THE GOODRX RESEARCHERS SAID MOST PEOPLE IN 20% OF THE MORE THAN 3,000 COUNTIES IN THE U.S. LIVE IN HOSPITAL DESERTS, WHICH THEY DEFINED AS AREAS REQUIRING A DRIVE OF MORE THAN 30 MINUTES TO REACH THE NEAREST HOSPITAL. THEY SAID THAT MORE THAN 40% OF COUNTIES ARE PHARMACY DESERTS, IN WHICH PEOPLE MUST DRIVE MORE THAN 15 MINUTES TO GET TO A PHARMACY. WHETHER A 15-MINUTE TRIP TO A PHARMACY IN A RURAL AREA CONSTITUTES THE HARDSHIP IMPLIED BY CALLING IT A “PHARMACY DESERT” MIGHT BE DEBATED.

THE COVID-19 PANDEMIC ALSO UNDERLINED HEALTHCARE ACCESS AND DISPARITY ISSUES, INCLUDING THE GAPS BETWEEN RURAL AREAS AND THE REST OF THE COUNTRY. KAISER HEALTH NEWS REPORTED IN SEPTEMBER THAT 1 IN 434 RURAL RESIDENTS HAD DIED OF COVID-19 SINCE THE PANDEMIC BEGAN COMPARED WITH 1 IN 513 URBAN RESIDENTS. AND COVID-19 VACCINATION RATES ARE MUCH LOWER IN RURAL AREAS. A STUDY BY SYRACUSE UNIVERSITY FOUND THAT AS OF EARLY AUGUST, 46% OF ADULTS WHO LIVED IN RURAL COUNTIES HAD BEEN VACCINATED COMPARED WITH 60% OF THOSE LIVING IN URBAN COUNTIES.

NOT A SUBSTITUTE

Peyin Hung, Ph.D., an assistant professor at the Arnold School of Public Health at the University of South Carolina who focuses on rural health disparities, says Dollar General’s move into healthcare is “a very good and promising strategy,” particularly in view of the pandemic. “Two years ago, I wouldn’t have been so optimistic.” But much depends on which healthcare services will be offered by Dollar General, the experts say. If the retailer’s offerings have a telehealth component, it could be a major boon because the pandemic “has really woken up technology expansion,” Hung says. A complicating factor is that many rural residents do not have access to broadband. To be successful, if Dollar General offered telehealth services, it would have to serve as a complement to local providers rather than a substitute, Hung says.

Slabach agrees that anything the retailer might do to provide services “would need to be done in collaboration with the established local medical communities.”

Richard Tarpey, MBA, a professor of management at Middle Tennessee State University and a former executive at HCA Healthcare, says retailers “can only offer limited nonurgent and preventative services. The larger contribution occurs when stores partner or open their own clinics that can provide a wider range of nonurgent, low-cost and convenient services within their stores,” such as the care offered at some CVS and Walgreens locations.

An in-store clinic “is really how you would best serve a rural population,” Tarpey adds, because “lack of primary care services results in people getting sicker and needing acute care.”

Walmart has opened or is in the process of opening a handful of clinics in Georgia, Arkansas and Florida, but Tarpey says the retailer lacks locations in “really deep healthcare deserts.” Walmart has started to send some mixed signals about its plans for getting into healthcare delivery. In an earnings call in August, CEO Doug McMillon said, “The work we did to build some clinics has been helpful, and I think we’ll have more clinics in the future. But the clinics aren’t the thing on its own.” McMillon talked about how Walmart was working to “stitch this whole thing together,” inclusive of telehealth, and “how you triage a customer when they start to interact with you to direct them to the place to get the right care at the right time.”

Perhaps Dollar General — and Walmart — can help meet rural healthcare needs, but they are not going to sweep away all the factors that have created the rural healthcare desert. In rural areas, “recruitment of providers is an extremely difficult thing these days,” Slabach notes. “It’s not easy to recruit someone to remote, rural areas.” Plus, the pandemic has put even more stress on providers, resulting in burnout, resignations and early retirement.

“THIS HAS BECOME THE REALITY WE’RE ALL ADJUSTING TO AT THE MOMENT,” SAYS SLABACH.

Susan Ladika, a frequent contributor to Managed Healthcare Executive®, is an independent journalist in Tampa, Florida, who writes about business and healthcare.
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Prescription digital therapeutics are FDA approved and available only by prescription. Their developers are aiming to get them covered by insurers.

By PETER WEHRWEIN
The world is awash in apps. There are almost 3 million of them on Google Play and 2 million on the Apple Store. Health-related apps make up a small fraction of this astounding total, but still number in the tens of thousands. Some are frivolous and others, merely innocuous, serving up reminders about your daily steps, the calorie counts of your meals or the best time to go outside for exposure to sunlight to crank up your vitamin D levels.

But there is also a more serious side to digital healthcare interventions that puts some of them on par with drugs and devices and stirs up a beehive of questions: the need for clinical trials, possible harms, coverage by insurers and whether they might help close healthcare disparities or wedge them open wider. A handful of developers are trying to separate themselves from the teeming masses of apps by getting their products approved by the FDA through a process designed for medical devices. Akili Interactive’s EndeavorRx, a game-based treatment for attention deficit hyperactivity disorder, was approved by the FDA in June 2020. A few months later, the agency approved NightWare’s namesake product, which uses an Apple Watch and iPhone and a proprietary algorithm to recognize when people are having nightmares and triggers a vibrating signal to jog them out of the disturbing dream.

Pear Therapeutics in Boston has three FDA-approved products: reSET for substance use disorder, reSET-O for opioid use disorder and Somryst for chronic insomnia. Proponents, particularly Pear, are positioning these FDA-approved products as “prescription digital therapeutics,” or PDTs, that clinicians will prescribe as they would a drug or a device. Corey McCann, M.D., Ph.D., president and CEO of Pear, says he is “not the PDT police” but offers up this definition of a PDT: “software to treat human disease.” McCann emphasizes that the software, not an ancillary device, is doing the treating so, for example, a continuous glucose monitor would not be a PDT under his definition. But the digital therapeutics are not recognized as a separate category in FDA regulations, so the dividing line between what is a PDT and what is not is open to interpretation.

Pear published a prescription digital therapeutic “digest” in October that listed just six PDTs: its three products, EndeavorRx, NightWare and Mahana Therapeutics’ Parallel, a PDT for irritable bowel syndrome.

Investors are plowing money into the companies that are developing PDTs. Mahana says it has raised a total of $81 million, including $61 million in Series B funding that it announced in August 2021. Pear announced in mid-November that it had landed $50 million in additional investment from an affiliate of Thimble Point Acquisition, a special purpose acquisition company that it plans to merge with so it can be traded publicly. Altogether the private investment in Pear and Thimble Point is expected to reach $175 million, according to company releases. McCann says Pear has 14 other products in the pipeline, and he talks about the company’s “ongoing partnership engine that continues to bring in some of the best assets that are available outside of Pear.”

The PDTs may put payment and coverage of digital therapeutics in a new light. Jeff Dunn, Pharm.D., MBA, a veteran of the PBM industry and a former executive with Magellan Rx, says the app developers traditionally targeted employers and employer groups and have steered clear of insurers and PBMs. A user-friendly app to help people lose weight might have been added to the benefits package as an inexpensive perk and signifier that the company cares about its employees’ health without too much concern about a return on investment. In some cases, Dunn says, the digital therapeutics have been seen as extension of disease and care management for groups of employees who are vulnerable to certain health problems. There might be some supporting evidence, but they haven’t gone through an FDA approval process and the goal is typically health or wellness. Dunn says that one of his previous employers owned a railroad, so a program to address musculoskeletal problems was added “because they had people out on the railyard.” Another company owned by that employer was considering Sleepio, a digital therapeutic for insomnia, and Daylight, a digital therapeutic for anxiety, because its employees are pilots.

Dunn says employers are being courted by the manufacturers of these types of digital therapeutics but “I don’t think employers are embracing this wholeheartedly.” Although the cost is typically moderate, there’s a lack of supporting evidence. t

“I think value-based agreements are what’s best for both the manufacturer and the payer because you have the data to be able to take the risk that’s in your best interest.”

—COREY McCANN, M.D., PH.D., PRESIDENT AND CEO OF PEAR THERAPEUTICS

Managed Healthcare Executive.com
“It’s like care management and disease management,” says Dunn. “How you report an ROI (return on investment) and outcomes and cost savings from those programs is a total black hole, and it always has been. I think it’s more of that.”

Patrick Gleason, Pharm.D., BCPS, FCCP, FAMCP, assistant vice president, health outcomes, at Prime Therapeutics, the PBM for 23 Blues plans, says several companies with digital therapeutics for diabetes are marketing themselves to large, self-insured employers. “The vendors who created them are going right to the self-insured employers and the human resources department and the people there who don’t have a lot of expertise in medical literature evaluation and convincing them that these are something that they should be paying for.”

Dunn says Pear and the other PDT makers want to get out of the gray area and circumventing insurers. “The Pears of the world,” he says, “they want coverage, they want reimbursement, they want to legitimize it, they want prescribers prescribing it — and they want to get (paid) more for it.”

**FDA APPROVALS**

Of course, the imprimatur of FDA approval is perhaps the surest way of garnering that legitimacy. Besides, as McCann points out, the only way to make a claim that a digital therapeutic treats a disease, as opposed to a vague claim of it helping with health and wellness, is FDA approval.

Pear’s first product, reSET, was approved in September 2017 as a treatment for alcohol, cocaine, marijuana and stimulant substance use disorders. The FDA press release heralding the approval noted some of the qualifications: that reSET is intended to be used with outpatient therapy and not intended for use as a treatment for opioid dependence (Pear’s follow-on PDT for opioid use disorder, reSET-O, was approved in December). The supporting clinical trial for reSET was a 12-week study that enrolled about 400 patients who either received standard therapy or standard therapy with the desktop version of reSET. Pear’s press release about the approval says the patients in the reSET arm of the study received a reduced amount of face-to-face counseling. The patient information sheet for the reSET notes, though, that it is not intended to reduce face-to-face time with the clinician. Data from that trial showed a marked difference in abstinence among the patients in the reSET arm compared with the control group (40.3% vs. 17.6%).

The efficacy claim for reSET-O is more limited. Results of the supporting clinical trial did not show the PDT as having an effect on drug use. Instead, the data from the trial showed that patients in the reSET-O group more likely to stay in a treatment program than patients in the control group (82.4% vs. 68.4%). McCann said that research since the FDA approval has shown that reSET-O does have an abstinence effect. Like reSET, reSET-O is supposed to be used in conjunction with treatment — in this case buprenorphine, an opioid that is prescribed to replace more harmful opioids — and contingency management therapy, a mode of therapy that links behavioral goals, such as abstaining from using opioids, to rewards.

Pear got reSET approved by the FDA by putting it on a regulatory pathway at the agency known as “de novo classification process” that was created in 1997 for novel medicaldevices posing low to moderate risk. ReSET-O and Somryst, Pear’s PDT for chronic insomnia, were approved under the FDA’s 510(k) approval process that allows devices on the market if the agency deems them as being “substantially equivalent” to previously approved “predicate” devices. ReSET was the predicate for reSET-O and Somryst.

NightWare, EndeavorRx and Mahana’s Parallel were also approved using the de novo pathway and had supporting evidence from clinical trials. NightWare was studied in a 30-day, sham-controlled study of 70 patients. The FDA said it reviewed multiple studies of EndeavorRx that included a total of more than 600 children. Mahana supported its application for Parallel with evidence from a trial of 558 patients. In November, the agency approved AppliedVR’s EaseVRx, a prescription virtual reality system that uses cognitive behavioral therapy to address chronic low back pain. That approval was based on a trial that enrolled 179 back pain patients.

Is it time for the FDA to develop a regulatory pathway explicitly for digital therapeutics? McCann is not a fan: “This is a pathway that we’ve made work three times, and I think you have seen the rest of the space start to make it work,” he says of de novo. “I think the argument for a bespoke pathway tends to come from organizations that haven’t made this pathway work.”

**INSURANCE COVERAGE**

FDA approval undoubtedly lends

**Continued on page 44**
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Cover story | Digital therapeutics

**Continued from page 42**

PDTs credibility. But like everything else in U.S. healthcare, PDTs are not really going to catch on — and the companies developing them are not going to be successful businesses — until insurers and other payers start covering them.

Pear has had recent success with persuading insurers to cover their PDTs. In October, the company announced that MassHealth, Massachusetts’s Medicaid program, intends to cover reSET and reSET-O. In September, it announced that it had entered into a value-based agreement with Prime for those two PDTs.

Neither Prime nor Pear is disclosing the exact terms of the deal, but the broad outlines are that Prime’s payment for the two PDTs will hinge, in part, on metrics measuring hospital inpatient stays, total healthcare cost, and physician engagement; one important feature of reSET and reSET-O is that they supply information about patients to their physician. ReSET and reSET-O are priced at about $1,600 per three-month period, so presumably Prime’s Blue plans will pay less if the agreed-upon metrics aren’t met.

McCann is nothing if not sanguine about value-based contracts — partly, he says, because of the data that PDTs generate by virtue of being digital. “It’s not that you do a non-value-based agreement and then you capitate and do a value-based agreement. That’s the way pharma works. That is not the way PDTs work,” McCann says. “I think value-based agreements are what’s best for both the manufacturer and the payer because you have the data to be able to take the risk that’s in your best interest.” He also mentions the results of a Pear-funded study published in *ClinicoEconomics and Outcomes Research* in October that showed $2,700 in cost savings per patient over nine months among those who “engaged” with reSET-O.

Gleason, who was involved in Prime’s negotiations with Pear, says value-based contracts for digital therapeutics flip the script. Value-based contracts for drugs put the onus on the payer to track the outcomes and metrics that factor into the value-based payment adjustment, he says. But in this case, the data collection and reporting are falling to Pear. That shift, says Gleason, saves Prime time and effort. Another advantage of value-based contracts for digital therapeutics is that, so far, they fall outside Medicaid’s best price rules, which can put constraints on the value-based cost adjustments that payers might otherwise seek.

Still, there’s a good deal of uncertainty about how exactly the Prime-Pear value-based contracting is going to play out. Prime is the PBM for 23 Blues plans, but it is up to those plans whether they will enter into the deal that Gleason and his colleagues have worked out with Pear.

**EQUITY ISSUES**

There are countless number of academics, consultants and “industry observers” who devote themselves to examining every nook and cranny of the U.S. pharmaceutical industry. Roger Vilardaga, Ph.D., is a member of a relatively small, but growing, group of experts studying digital therapeutics. Vilardaga, an assistant professor in the Department of Psychiatry and Behavioral Sciences at Duke University, says the worry several years ago among behavioral researchers and others was that regulation might stifle the innovation of digital therapeutics. Now with the flood of healthcare apps, the concern has shifted to, at best, lack of efficacy of many digital therapeutics, to, at worst, their being misleading and harmful.

Lack of efficacy when it comes to forever problems like losing weight or getting more exercise would be nothing new. But in the context of a problem like opiate addiction, lack of efficacy and possible harm converge, Vilardaga says. “If you have an opiate addiction and you recommend something like crystal therapy or positive thinking, it can be harmful for the individual to pursue those options rather than legitimate, evidence-based alternatives.”

Vilardaga was the lead author of a study published last year in *Current Addiction Reports* that reviewed 59 opioid-related apps available on Google Play. More than half of the apps had data privacy language that fell short of the criterion in the American Psychiatric Association’s App Evaluation Model and just one — reSET-O — met all eight of the criteria of quality in the association’s app model. Running digital therapeutics through the gantlet of FDA approval will presumably help address some of the efficacy issues, although the current proportions are sobering: a handful of FDA-approved PDTs versus the 50,000-plus apps. Vilardaga also pins some hope on the creation of libraries of apps, curated by independent experts, or an accreditation process.

Winnowing for efficacy and safety would begin to solve one set of problems with apps and digital therapeutics, but not others. “Just because a device is evidence-based and has been regulated doesn’t mean it is going to promote health equity,” Vilardaga says. With apps and digital therapeutics, there’s the barrier of getting people to actually use them. Access to Wi-Fi and high-speed internet is certainly a factor, but so are the products themselves — the language they use, the design elements they feature, the intuition they tap into. For pharmaceuticals, there are decades of experience and study about how to deliver and get people to take prescribed medication. Vilardaga calls it “implementation science” and says it is lacking for digital therapeutics. “I think there’s implementation science research that needs to be conducted head-on to be able to integrate these digital therapeutics into the actual, real-world practices.”

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For your appropriate members with uncontrolled moderate-to-severe atopic dermatitis (AD)

**INDICATION**

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATION**: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity**: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

**Conjunctivitis and Keratitis**: Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

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

IL, interleukin.

**APPROVED FOR A BROAD AGE RANGE**

6+ YEARS OF AGE

**RAPID AND SUSTAINED RESULTS**

in adults

**DEMONSTRATED LONG-TERM SAFETY PROFILE**

in adults

- **DUPIXENT IS A DUAL INHIBITOR OF IL-4 AND IL-13 SIGNALING**
- **DUPIXENT AVOIDS BROAD IMMUNOSUPPRESSION**
  – It is unknown if DUPIXENT will influence the immune response against helminth infections

**INDICATION**

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

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**Conjunctivitis and Keratitis**: Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

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

IL, interleukin.
IN A CHRONIC SYSTEMIC DISEASE...

Review the data and important considerations for this long-term treatment

**Adult safety profile across 52 weeks generally consistent with Week 16**

Most common adverse reactions (incidence ≥1% at Week 16) in adult patients with atopic dermatitis are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

The safety profile in children and adolescents through Week 16 was similar to that of adults with atopic dermatitis.

**TRIAL RESULTS:** The primary endpoint in Trials 3 and 6 was change from baseline in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and ≥2-point improvement at Week 16 (39% of adults treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 3, P < 0.0001; and 24% of adolescents treated with DUPIXENT vs 2% with placebo in Trial 6, P < 0.001). In Trial 8, the primary endpoint was change from baseline in the proportion of subjects with an IGA 0 or 1 at Week 16 (39% of children ≥30 kg treated with DUPIXENT + TCS vs 10% with placebo + TCS, and 30% of children <30 kg treated with DUPIXENT + TCS vs 13% with placebo + TCS). Other endpoints included change from baseline in the proportion of subjects with EASI 75% at Week 16 (improvement of ≥75%: 69% of adults treated with DUPIXENT + TCS vs 23% with placebo + TCS in Trial 3, P < 0.0001; 42% of adolescents treated with DUPIXENT vs 8% with placebo in Trial 6, P < 0.001; 75% of children ≥30 kg treated with DUPIXENT + TCS vs 26% with placebo + TCS, and 75% of children <30 kg treated with DUPIXENT + TCS vs 28% with placebo + TCS in Trial 8); and itch reduction defined by ≥4-point improvement in the Peak Pruritus NRS at Week 16 (59% of adults treated with DUPIXENT + TCS vs 22% with placebo + TCS in Trial 3, P < 0.0001; 37% of adolescents treated with DUPIXENT vs 5% with placebo in Trial 6, P < 0.001; 63% of children ≥30 kg treated with DUPIXENT + TCS vs 13% with placebo + TCS, and 54% of children <30 kg treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 8). Trial 3 also assessed endpoints at Week 52: IGA: 36% of adults treated with DUPIXENT + TCS vs 13% with placebo + TCS; EASI-75: 65% of adults treated with DUPIXENT + TCS vs 13% with placebo + TCS; Peak Pruritus NRS: 51% of adults treated with DUPIXENT + TCS vs 13% with placebo + TCS; P < 0.0001. In Trial 3, improvement was seen as early as at Week 2, with EASI-75 achieved by ≥20% of adults treated with DUPIXENT + TCS vs ≥9% with placebo + TCS (post hoc analysis), and itch reduction (≥4-point improvement in the Peak Pruritus NRS) achieved by ≥18% of adults treated with DUPIXENT vs 2% with placebo in Trial 3, P < 0.0001.2, 4-6

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS (cont’d)**

**Reduction of Corticosteroid Dosage:** Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

**Atopic Dermatitis Patients with Comorbid Asthma:** Advise patients not to adjust or stop their asthma treatments without consultation with their physicians.

**Parasitic (Helminth) Infections:** It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

**EASI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment; NRS, numerical rating scale; TCS, topical corticosteroids.**
SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in < 1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Please see additional Warnings and Precautions in the Prescribing Information and in the Brief Summary included and Important Safety Information throughout.

Hypersensitivity

The safety profile in children and adolescents through Week 16 was similar to that of adults with atopic dermatitis. In an open-label extension study, the long-term safety profile of DUPIXENT in adolescents and children observed through Week 52 was consistent with that seen in adults with atopic dermatitis.

IMPORTANT SAFETY INFORMATION (cont’d)

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 1% at Week 16) in adult patients with atopic dermatitis are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. The safety profile in children and adolescents through Week 16 was similar to that of adults with atopic dermatitis. In an open-label extension study, the long-term safety profile of DUPIXENT in adolescents and children observed through Week 52 was consistent with that seen in adults with atopic dermatitis.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

• Pregnancy: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Healthcare providers and patients may call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or obtain information about the registry. Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.

• Lactation: There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

BSA, body surface area; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

Please see Brief Summary of full Prescribing Information on the following pages.
DUPIXENT® (dupilumab) injection, for subcutaneous use Rx only

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPLEXTEN can be used with or without topical corticosteroids.

4 CONTRAINDICATIONS

DUPLEXTEN is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPLEXTEN in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPLEXTEN [see Adverse Reactions (6.1, 6.2)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPLEXTEN. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see Adverse Reactions (6.1)].

Advisors to patients to report new onset or worsening eye symptoms to their healthcare provider.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPLEXTEN. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in inhaled corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Patients with Comorbid Asthma

Advisors to patients with atopic dermatitis who have co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPLEXTEN will influence the immune response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with DUPLEXTEN. If patients become infected while receiving treatment with DUPLEXTEN and do not respond to antihelminthic treatment, discontinue treatment with DUPLEXTEN until the infection resolves.

6 ADVERSE REACTIONS

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

- Hypersensitivity [see Warnings and Precautions (5.1)]
- Conjunctivitis and Keratitis [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPLEXTEN in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 14172 subjects were treated with subcutaneous injections of DUPLEXTEN, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPLEXTEN for at least 1 year in the development program for moderate-to-severe atopic dermatitis. Trials 1, 2, and 3 compared the safety of DUPLEXTEN monotherapy to placebo through week 16. Trial 3 compared the safety of DUPLEXTEN + TCS to placebo + TCS through Week 52.

Weeks 0 to 16

In DUPLEXTEN monotherapy trials (Trials 1, 2, 3, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPLEXTEN 300 mg Q2W and placebo groups. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPLEXTEN 300 mg Q2W monotherapy groups, and in the DUPLEXTEN + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPLEXTEN Monotherapy*</th>
<th>DUPLEXTEN + TCS*</th>
<th>Injection site reactions</th>
<th>Conjunctivitisa</th>
<th>Blepharitisa</th>
<th>Oral herpes</th>
<th>Keratitis a</th>
<th>Eye pruritusa</th>
<th>Other herpes simplex virus infectionb</th>
<th>Dry eye</th>
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<td></td>
<td>51 (10)</td>
<td>28 (5)</td>
<td>11 (10)</td>
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<td>2 (1)</td>
<td>20 (4)</td>
<td>1 (1)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in ≥1% of the DUPLEXTEN Monotherapy Group or the DUPLEXTEN + TCS Group in the Atopic Dermatitis Trials through Week 16

*Pooled analysis of Trials 1, 2, and 4.

†Analysis of Trial 3 where subjects were on background TCS therapy.

‡DUPLEXTEN 600 mg at Week 0, followed by 300 mg every two weeks.

§Concomitant clusters include conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

¶Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

‖Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex ophthalmica externa, and herpes virus infection, but excludes eczema herpeticum.

‡‡Safety through Week 52 (Trial 3)

In the DUPLEXTEN with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in DUPLEXTEN 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPLEXTEN because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

The safety profile of DUPLEXTEN + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The safety of DUPLEXTEN was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPLEXTEN in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPLEXTEN was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPLEXTEN in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPLEXTEN observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Children with Atopic Dermatitis (6 to 11 Years of Age)

The safety of DUPLEXTEN with concomitant TCS was assessed in a trial of 368 subjects 6 to 11 years of age with severe atopic dermatitis (Trial 8). The safety profile of DUPLEXTEN in these subjects through Week 16 was similar to the safety profile from studies in trials in adults and adolescents with atopic dermatitis.

The long-term safety of DUPLEXTEN + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (Trial 7). Among subjects who entered this trial, 107 had moderate and 72 (20%) had severe atopic dermatitis at the time of enrollment in Trial 7. The safety profile of DUPLEXTEN + TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in Trial 8. The long-term safety profile of DUPLEXTEN + TCS observed in pediatric subjects was consistent with that seen in adults and adolescents with atopic dermatitis [see Pediatric Use (8.4)].

Specific Adverse Reactions

Conjunctivitis and Keratitis

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 1% of the DUPLEXTEN 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). In DUPLEXTEN atopic dermatitis monotherapy trials (Trials 1, 2, and 4) through Week 16, keratitis was reported in <1% of the DUPLEXTEN group (1 per 100 subject-years) and in <1% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis DUPLEXTEN + TCS trial (Trial 3), keratitis was reported in 4% of the DUPLEXTEN + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see Warnings and Precautions (5.2)].

Ecema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPLEXTEN groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPLEXTEN groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 52-week atopic dermatitis monotherapy trials. In the 52-week DUPLEXTEN + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPLEXTEN + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).
Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUXIPENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis [see Clinical Pharmacology (12.3) in the full prescribing information].

Eosinophilia

DUXIPENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils were 150 cells/mm³ and 50 cells/mm³, respectively. Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mm³) was similar in DUXIPENT and placebo groups.

Treatment-emergent eosinophilia (≥500 cells/mm³) was reported in <2% of DUXIPENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with atopic dermatitis (Trial 3), CV thomboembolic events (CV deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUXIPENT + TCS group, 0 (0.0%) of the DUXIPENT group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, and the patient’s underlying disease.

For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies to dupilumab in other studies or to other products may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUXIPENT 300 mg Q2W for 52 weeks developed antibodies with neutralizing activity; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies. Similar results were observed in pediatric subjects (6–<18 years) with atopic dermatitis who received DUXIPENT 200 mg Q2W or 300 mg Q4W for 16 weeks.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUXIPENT 150 mg Q2W for 16 weeks developed antibodies to dupilumab, ~3% exhibited persistent ADA responses, and ~5% had neutralizing antibodies. Regardless of age, ~2 to 4% of subjects in the placebo group were positive for antibodies to DUXIPENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

The antibody responses detected in both DUXIPENT and placebo subjects were mostly low. In subjects who received DUXIPENT, development of higher titer antibodies to dupilumab was associated with lower serum dupilumab concentrations [see Clinical Pharmacology (12.3) in the full prescribing information].

Two adult subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUXIPENT therapy [see Warnings and Precautions (5.1)].

6.3 Postmarketing Experience

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

Skin and cutaneous tissue disorders: Facial Rash

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUXIPENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which adult subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUXIPENT administration, subjects were vaccinated with Menomune vaccines. Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUXIPENT during pregnancy.

Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoin-study/du/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUXIPENT use in pregnant women have identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUXIPENT may be transferred to the developing fetus. In the reported pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) [see Data]. The estimated background risk of major birth defects and miscarriage for the unselected populations are unknown. All pregnancies are inherently at risk of birth defect, loss, or other adverse outcomes. 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.

Animal Data

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered 3378.8 mg/kg of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on fetal or neonatal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUXIPENT and any potential adverse effects on the breastfed child from DUXIPENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUXIPENT have been established in pediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis.

Use of DUXIPENT in this age group is supported by Trial 6 which included 251 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis and Trial 8 which included 373 children aged 6 to 11 years with severe atopic dermatitis. The safety and efficacy were generally consistent between pediatric and adult patients [see Adverse Reactions (6.1) and Clinical Studies (14.1) in the full prescribing information].

Use is also supported by Trial 7, an open-label extension study that enrolled subjects who completed Trials 6 and 8. Trial 7 included 136 adolescents from Trial 6 and 110 children from Trial 8. All adolescents and children entered a blinded trial at enrollment into the extension study. Trial 7 included 84 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis at enrollment. No new safety signals were identified in Trial 7 [see Adverse Reactions (6.1)].

Safety and efficacy in pediatric patients ≥6 years of age with atopic dermatitis have not been established.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUXIPENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects [see Clinical Pharmacology (12.3) in the full prescribing information].

10 OVERDOSE

There is no specific treatment for DUXIPENT overdose. In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUXIPENT during pregnancy. Encourage participation in the registry [see Use in Specific Populations (8.1)].

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUXIPENT prior to use. Advise patients to follow sharps disposal recommendations [see Instructions for Use].

Hypersensitivity

Advise patients to discontinue DUXIPENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions [see Warnings and Precautions (5.1)].

Contraindications and Geriatric

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see Warnings and Precautions (5.2)].

Reactions in Corticosteroid-Dependent Asthma

Inform patients not to discontinue systemic, topical, or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see Warnings and Precautions (5.5)].

Patients with Comorbid Asthma

Advise patients with atopic dermatitis who have comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see Warnings and Precautions (5.6)].
An oral health problem is often the body’s canary in the coal mine. According to the Academy of General Dentistry, more than 90% of human diseases — everything from cancer to heart disease to infectious diseases — first present as symptoms that affect the mouth.

But in the United States when it comes to insurance coverage, oral health and dental care have been severed from other healthcare coverage. According to the American Dental Association (ADA) Health Policy Institute, one-third of adults and about 1 in 10 children don’t have dental coverage. In some cases, people elect not to have coverage, calculating that their out-of-pocket costs for the routine services covered by a dental insurer will be less than the cost of a year’s worth of monthly premiums. “The benefit is typically sold separately, and not everyone purchases it,” notes Adam C. Powell, Ph.D., president of Payer+Provider Syndicate, a healthcare consulting company in Boston. “As the costs of dental care are typically much lower than the costs of medical care, many people cover the costs of dental care out of pocket instead of buying dental insurance.”

Dental care is another fissure in American healthcare that both causes and reflects deeply rooted inequities. Black and Latino children and adults and people who live in historically underserved urban and rural communities report lower rates of dental care than the general population. Among adults aged 20 to 64 years, nearly twice as many Black and Mexican American adults have untreated cavities as White adults. A shortage of dentists in low-income neighborhoods and family financial constraints are among the chief obstacles preventing children in lower-income families from receiving dental care, says Fred DiOrio, D.M.D., dental director of government programs at Horizon Blue Cross Blue Shield of New Jersey.

Employer offerings
More than 200 million Americans have some kind of dental care coverage, and about half of employers offer their employees a dental plan. Dental insurance coverage offered by employers is traditional noncatastrophic coverage that provides discounts and full coverage for preventive services such as cleanings, but limited coverage for acute services, Powell says. Most plans offer comprehensive coverage for diagnostic and preventive care and varying levels of coverage for restorative care such as fillings, crowns, dentures and oral surgical procedures. Orthodontia and cosmetic dentistry are covered less frequently.

While many plans have an annual maximum benefit of up to $1,000 or $1,500, most consumers rarely exceed their annual maximum benefit from year to year, according to Scott Towers, president of the dental division of Anthem. Edward A. Murphy, MBA, executive vice president of government programs at Horizon Blue Cross Blue Shield New Jersey.
THERE MAY BE A HIDDEN CULPRIT IN IgA NEPHROPATHY

A better understanding of the pathophysiology of IgA-related autoimmune diseases, including nephropathy, may help provide targets for future treatment exploration. Investigate further at HiddenCulprit.com
Oral and dental health is crucial. But access to coverage is spotty.

Advantage plans include some of the increasingly popular Medicare hearing services. However, most of the versions limited the expansion to just vision and hearing services. A later version would have expanded Medicare coverage to cover dental services as well as preventive and restorative services like fillings. Medicaid pays so many plans pay, so many dentists turn away patients whose care would be paid at Medicaid rates, or they restrict the number of Medicaid patients they see, Towers says. As of 2019, less than half (43%) of dentists in the United States accepted Medicaid or the Children’s Health Insurance Program (CHIP), according to the ADA Health Policy Institute.

Traditional Medicare doesn’t cover dental care. One version of Democrats’ Build Back Better legislation would have expanded Medicare to cover dental services as well as vision and hearing services. A later version limited the expansion to just hearing services. However, most of the increasingly popular Medicare Advantage plans include some dental care coverage. The benefits can include preventive services, such as cleanings, as well as more comprehensive benefits including restorations and crowns, says Quinn Dufurrena, D.D.S., J.D., chief dental officer at United Concordia Dental, a dental insurer headquartered in Camp Hill, Pennsylvania.

Some trends are pointing toward more Americans gaining dental coverage. “Within the private sector, cost tends to be the biggest obstacle to coverage and payers continue to innovate and expand cost-effective benefit plans tailored to a wide audience, including underserved communities,” Towers says. Some health plans are embedding benefits in select plans to encourage whole-person health. In addition, some plans are increasing annual maximums to provide broader benefits. DiOrio says dental practices are increasingly willing to enter into value-based arrangements with insurers. Similar to value-based arrangements in other areas of American healthcare, these dental value-based arrangements tie payment to quality-of-care measures and other factors.

The ACA has extended dental insurance coverage to more Americans by virtue of Medicaid expansion, although the low payment rates often create an insurmountable barrier to actually getting care. Thirty-eight states and the Washington, D.C., have expanded Medicaid under the ACA. Moreover, in many states, the number of people covered by Medicaid has increased since the beginning of the COVID-19 pandemic last year because people lost jobs that provided employer-based health and dental insurance. But for adults, dental coverage isn’t one of the ACA essential health benefits, so it doesn’t need to be included in the coverage provided by the health plans sold on the ACA exchanges. Dental coverage is an ACA essential health benefit for children so dental coverage for people aged 18 years or younger must be available, either as part of the health plan or as a stand-alone plan.

The integration of medical and dental benefits results in better health outcomes, says Susan Fleischman, M.D., chief medical officer at Blue Shield of California. Based on the insurer’s review of groups with both medical and dental coverage, the per-member, per-month cost of healthcare has been consistently 3% to 6% lower in plans that offer medical and dental coverage together than in those that cover only medical services.

But adding benefits to health plans increases premiums. “Given the relatively modest cost of most dental care relative to medical care, many people can forgo dental insurance without experiencing substantial additional financial risk,” Powell says.

Karen Appold is a medical writer who lives in the Lehigh Valley region of Pennsylvania.
Specialty pharmacy is a growing part of the pharmacy business, and it is becoming increasingly competitive and complicated as therapies get more expensive — some with price tags in the seven figures. Speakers at Asembia’s 2021 Specialty Pharmacy Summit discussed the size and expense of the industry but also delved into issues of health equity, health literacy and making it easier for patients to navigate healthcare, including specialty pharmacy services.

More than 4,000 people attended the meeting at the Wynn Las Vegas hotel in Las Vegas. Attendees were required to provide proof of full vaccination against COVID-19 and masks were required indoors. The program for the meeting listed a total of 75 sponsors, tiered into diamond, platinum, gold and silver levels, and 121 exhibitors.

Here are summaries of several of the sessions:

**Specialty is a growing share of the pharma market. PBM, health systems are vying for that larger slice of the pie.**

Specialty pharmacy, once a niche in the pharmaceutical industry, is on a trajectory to account for more than half of the industry’s revenues and that growth has set off fierce competition for control of the specialty drug pricing and distribution, a pair of industry experts told attendees at the opening session of the meeting’s first full day.

“Specialty drugs today are about 40% of the entire pharmacy industry’s revenues,” said Adam Fein, Ph.D., an expert on drug pricing and distribution and CEO of Drug Channels Institute. Within three to four years, that proportion will likely increase to 50%, said Fein. Although independent specialty pharmacies still account for the largest share of the specialty industry, healthcare providers now account for the second-largest share, according to Fein.

“In 2015, 1 out of 10 specialty pharmacies was run by a hospital or a physician practice. Today, it’s 4 out of 10,” Fein told conference attendees. That shift has largely coincided with the larger trend of vertical integration that has affected many aspects of American healthcare, he observed.

Doug Long, MBA, vice president of industry relations at IQVIA, also spoke at the first session.

Fein noted that the three largest PBM in the United States — CVS Caremark, OptumRx and Express Scripts — now manage more than 75% of prescription claims.

The PBMs have moved into ownership of specialty pharmacies because most manufacturers launch their specialty drugs in narrow networks, Fein explained. Meanwhile, the majority of large hospitals now have their own in-house specialty pharmacies and use them as the driver for their benefit plans. The large hospitals and their health systems “learned from what the PBMs are doing to channel patients into their business — and, in fact, the majority of the prescriptions filled by these specialty pharmacies are coming from, are written by, the prescribers who work at the health systems,” said Fein.

“Everyone is figuring this out,” he continued, “and this is where the battle is happening between these different vertically integrated systems,” he added.

Fein also discussed the controversial 340B drug pricing program, which requires drugmakers to sell their products to some hospitals and healthcare organizations at discounted prices. Supporters say it helps reduce the cost of...
healthcare and increase access to disadvantaged patients. Critics say healthcare systems have exploited the program to get drugs at cheaper prices and increase their revenues.

Data from IQVIA presented at the session showed that, excluding all discounts from the program, buying through 340B accounts for more than 40% of all hospital purchasing and about 13% of all dollars in retail pharmacy.

“That means those prescriptions generate above-average profits for pharmacies, often profits that are four to five times as much gross profit dollars per script as a normal commercial script, Medicare Part D script,” said Fein.

Overall, the growth of 340B is being driven by specialty drugs, and the program’s economics heavily impact each facet of the specialty pharmacy channel, Fein noted. On a net sales basis, the 340B program is now bigger in some ways than Medicaid, he said.

With regard to the retail specialty market, recent data show a decline, due in large part to two leading HIV drugs losing patent protection, explained Long. Therapies for HIV are among the top 10 specialty drug categories in the retail market.

Long also shared IQVIA data that showed an increased demand for mental health and pain drugs during the COVID-19 pandemic.

Start early, be clear and be ready for the FDA: Some tips for gaining market access

Collaboration and communication are imperative for pharmaceutical companies to improve market access of their products, said members of a panel on market access.

Experts Dave MacLeod, Erin Mistry, M.S., and Robert Rouse, M.S., offered their perspectives on best practices for market access.

MacLeod is head of global patient services and commercial distribution at Amylyx Pharmaceuticals in Plainville, Massachusetts; Mistry is senior vice president, head of payer strategy, government affairs and trade relations at CorMedix in Berkeley Heights, New Jersey; and Rouse is head of U.S. market access for CSL Behring, whose parent company, CSL Limited, is headquartered in Melbourne, Australia. Tony Lanzone, MBA, managing director, value, access and HEOR (health economics and outcomes research) at Syneos Health in Morrisville, North Carolina, moderated the discussion.

As part of effective communication, the panelists stressed the importance of consistent, clear messaging throughout all levels of the organization and of maintaining a consistent definition of value when working with different stakeholders. They said the definition of value should be consistent, but when it comes to engaging patient advocacy groups, providers or government payers, approaches may need to be tailored.

Value is also not confined to one time point in the product’s lifecycle and can be complex, MacLeod, Mistry and Rouse noted. Defining value at clinical, precommercial and commercial stages is essential and relies upon effective collaboration and communication.

Market access is not restricted to contracts, MacLeod noted. “If you’re preparing to bring a drug to market and your regulatory team is putting together an NDA (new drug application) and a label, you want your market access team in there to provide insights,” he told the meeting attendees. “Not to tell them how to do it, but to let them know what is going to read back out from the payers, what are they going to understand and what are they going to see to give you the broadest label you can get.”

Keeping regulatory changes in mind is also crucial, advised Mistry. Understanding the regulatory changes that the FDA might make and keeping tabs on the issues that CMS is prioritizing — such as health equity and patient outcomes — can be hugely beneficial to market access efforts, she added.

Characterizing market access as a policy function, Mistry said that “if you don’t have the folks that are knowledgeable about policy sitting at the table with you when you’re in discussions, then I think that that’s a missed opportunity.”

Companies seeking FDA approvals teams need to be prepared to make a strong case for their products, said Mistry: “Your regulatory team needs to know what to argue to the FDA to make it the most commercially viable product on the market.”

Rouse discussed how the perceptions and calculations of a product’s value may vary with the customer. He also said the work needed to anticipate how a product might be valued by various stakeholders can start even when a product is still in phase 1 or 2 trials.

The direction (and amounts) of revenue and payment in the American healthcare system can be baffling, particularly with respect to the payment for pharmaceuticals, the panelists noted.

“I think that’s what a market access function brings internally. Marketing, sales, medical affairs — you can educate your teams on how the flow of money works,” said Mistry.

Granular and specific data that are concise and digestible play a role in effective communication, the panelists noted. Physician-to-physician communication about the value of a product is key, in Mistry’s view.

Sometimes providers will distrust the payer or manufacturer perspective on a product’s value, Rouse added. Peer exchanges among providers or input from patient advocates can help fill this communication gap.

“You can’t be rigid in how you approach market access, or a product launch, or even a product that’s further down in its lifecycle, because there are always going to be challenges,” summarized MacLeod. Alignment in messaging and multi-
partnered communication can help clear these hurdles, he said.

**No need to dread REMS**

“Fear not” was the takeaway message from members of a panel on Risk Evaluation and Mitigation Strategies (REMS) programs.

In fact, REMS can greatly contribute to a product’s success and physician uptake, said Steve Granzyk, vice president, pharmacy relations and business strategy, at AcariaHealth, and Tiffany Abraham, president of Abidance Solutions.

The main goal of REMS is ensuring patient safety and showing a product’s benefits outweigh the risks, said Granzyk and Abraham. The FDA requires manufacturers to create and maintain the program “when there are medications that have a patient need, but there are ... risks around that and safety concerns for the patients,” explained Abraham.

REMS programs have stirred up some controversy. Drugmakers have been accused of using the programs and exploiting the limited distribution requirements for anti-competitive purposes.

But at the Asembia meeting, Abraham talked about the programs’ benefits to patients, including the reductions in the frequency and severity of side effects.

The FDA “recommends what the REMS will be and what certain components will be; how complex it will be. But the manufacturer truly works to create that and collaborates with the FDA leading up to drug launch,” Abraham said.

A fraction of REMS programs (10%) requires only a medication guide, whereas more complex programs require elements to assure safe use (ETASU). ETASU can include enrollment registries, patient assessment prior to initiation and other requirements, Abraham noted.

Pharmacies and healthcare settings come into the picture when restricted distribution is mandated in a REMS program, Abraham told the Asembia meeting attendees. Some programs may require pharmacies or healthcare providers to take certain steps before a drug is dispensed or administered.

Data collection is a component and, periodically, REMS programs are checked for compliance, and the results are sent to the FDA, explained Granzyk and Abraham. The FDA can also assess compliance randomly. Manufacturers may also have audit REMS participants.

“From a specialty pharmacy perspective, you’re always looking to limit the number of branches to what you actually need and to the extent that they’re allowed in the pharma program,” said Granzyk adding that his benefits pharma as well, because it limits the diversion of product.

REMS programs boost provider confidence in a new drug because they provide that extra layer of data, confidence and assurance, he explained. In addition to education, Granzyk highlighted the importance of internal collaboration between departments and innovation to limit errors and boost efficiency.

**Specialty pharmacy: What’s coming down the pike?**

George Van Antwerp, MBA, leads Deloitte’s “Future of Pharmacy” efforts. At the Asembia meeting, he offered a peek into that future.

Continued care transformation to a digital or virtual service will enable a more precise focus on both the consumer and data in the future, Van Antwerp said. The shift may impact how prescriptions are written — potentially by pharmacists instead of providers — and help shape the role of a pharmacist in the healthcare world.

**“Everyone is figuring this out ... the battle is happening between these different vertically integrated systems.”**

ADAM FEIN, PH.D., AN EXPERT ON DRUG PRICING AND DISTRIBUTION AND CEO OF DRUG CHANNELS INSTITUTE

“The idea of integration of technology with drug, it drives a very fascinating picture of the future,” said Van Antwerp, a Deloitte managing director who focuses on pharmacy and PBM issues.

Thinking about the causes of disruptive change, Van Antwerp and his Deloitte colleagues considered a range of technologies that may come into play: nanotechnology, quantum computing, nutraceuticals and CRISPR gene editing.

Van Antwerp asked the Asembia attendees to contemplate a future for drug development that would be based on simulations and at-home drug manufacturing using 3D printers. Although precision medicine tends to be thought of treatments guided by genomic testing, Van Antwerp mentioned the possibility of individualizing the diets of patients with diabetes to their microbiomes.

Virtual remote monitoring could shift resources from treatment to preventive measures, Van Antwerp said. He also said he envisions a larger role for pharmacists.

Along with these innovations will come myriad challenges, Van Antwerp acknowledged. As care becomes more digitally based and potentially more complex, some patients may not be able to keep up.

Van Antwerp noted that 80% of healthcare costs are the result of human behaviors and social determinants of health. “You can think about how payment models could evolve to say, ‘Are there things that you’re born with, and you can’t do anything about?’ We should be covering that cost from a society perspective versus the (healthcare costs that) you can influence or your employer can influence or your health plan can influence.”
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For the treatment of adults with schizophrenia or bipolar I disorder

Indications
LYBALVI is indicated for the treatment of:
- Schizophrenia in adults
- Bipolar I disorder in adults
- Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
- Maintenance monotherapy treatment

Important Safety Information

Boxed Warning: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Contraindications: LYBALVI is contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal. If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis, including stroke, transient ischemia attack, and fatalities. See Boxed Warning above.

Precipitation of Severe Opioid Withdrawal in Patients who are Physiologically Dependent on Opioids: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

Vulnerability to Life-Threatening Opioid Overdose: Attempting to overcome opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI. In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia, discontinue LYBALVI. Opioids should be administered by properly trained individual(s) and patient should be continuously monitored in a setting equipped and staffed for cardiopulmonary resuscitation. Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome, a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation, intensive symptomatic treatment, and close monitoring.

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a potentially fatal condition reported with exposure to olanzapine, a component of LYBALVI. Symptoms include a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue if DRESS is suspected.

Metabolic Changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Measure weight and assess fasting glucose and lipids when initiating LYBALVI and monitor periodically.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, or after discontinuation. Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. If signs and symptoms of TD appear, drug discontinuation should be considered.

Orthostatic Hypotension and Syncope: Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.

Falls: LYBALVI may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls, and consequently, fractures or other injuries. Assess patients for risk when using LYBALVI.

Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases): Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count or history of leukopenia or neutropenia. Discontinue LYBALVI if clinically significant decline in WBC occurs in the absence of other causative factors.

Dysphagia: Use LYBALVI with caution in patients at risk for aspiration.

Seizures: Use LYBALVI with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Because LYBALVI may cause somnolence, impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including motor vehicles, until they are certain that LYBALVI does not affect them adversely.

Body Temperature Dysregulation: Use LYBALVI with caution in patients who may experience conditions that increase core body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, was associated with constipation, dry mouth, and tachycardia. Use LYBALVI with caution with other anticholinergic medications and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: LYBALVI elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate prescribing information for a description of the risks for these products.

Most common adverse reactions observed in clinical trials were:

- Schizophrenia (LYBALVI): weight increased, somnolence, dry mouth, and headache
- Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

Concomitant Medication: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Concomitant use of LYBALVI is not recommended with strong CYP3A4 inducers, levodopa and dopamine agonists. Reduce dosage of LYBALVI when using with strong CYP1A2 inhibitors. Increase dosage of LYBALVI with CYP1A2 inducers. Use caution with diazepam, alcohol, other CNS acting drugs, or in patients receiving anticholinergic (antimuscarinic) medications. Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with LYBALVI. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LYBALVI during pregnancy.

Renal Impairment: LYBALVI is not recommended for patients with end-stage renal disease (eGFR of <15 mL/minute/1.73 m²).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of Full Prescribing Information, including Boxed Warning, for LYBALVI on the following pages.
INDICATIONS AND USAGE
LYBALVI is indicated for the treatment of:
- Bipolar I disorder in adults
- Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
- Maintenance monotherapy treatment

CONTRAINDICATIONS
LYBALVI is contraindicated in patients:
- who are using opioids
- who are undergoing acute opioid withdrawal

LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that necessitates the use of antipsychotics, and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment as possible. If signs and symptoms of tardive dyskinesia appear in a patient on LYBALVI, drug discontinuation should be considered. However, some patients may require treatment with LYBALVI despite the presence of the syndrome.

Oral DRUG INTERACTIONS:
- It is recommended to avoid concurrent use of LYBALVI with strong CYP3A4 inhibitors or moderate CYP3A4 inducers and to use with caution in patients who are using moderate CYP3A4 inhibitors or strong CYP3A4 inducers.
- LYBALVI's opioid blockade with high or repeated doses of exogenous opioids (e.g., because of ineffective analgesia or opioid withdrawal symptoms) could lead to life-threatening or fatal opioid intoxication (e.g., respiratory arrest, circulatory collapse), particularly if LYBALVI therapy is interrupted or discontinued, subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Informed patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI.

In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia:
- Discontinue LYBALVI.
- Opioids should be administered by individual(s) trained in the use of anesthetic drugs and the management of the respiratory effects of opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation, and
- Appropriately trained personnel should continuously monitor the patient in a setting equipped and staffed for cardiopulmonary resuscitation.

For recommendations on starting opioids in LYBALVI-treated patients in non-emergent situations, see DRUG INTERACTIONS section.

Risk of Resuming Opioids in Patients with Prior Opioid Use
Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Acute renal failure. If NMS is suspected, immediately discontinue LYBALVI and provide intensive symptomatic treatment and monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with exposure to olanzapine, a component of LYBALVI. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic compromise such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue LYBALVI if DRESS is suspected.

Metabolic Changes: Atypical antipsychotic drugs, including LYBALVI, have been associated with metabolic changes that include hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with LYBALVI should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Patients starting treatment with LYBALVI should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Antipsychotics have caused adverse alterations in lipids. Patients starting treatment with LYBALVI should undergo fasting lipid profile testing at the beginning of treatment and periodically during treatment.

Weight gain has been observed with use of antipsychotics. Monitor weight prior to initiating LYBALVI and frequently thereafter.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

Oral NMS is a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue LYBALVI and provide intensive symptomatic treatment and monitoring.
Monitor orthostatic vital signs in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypoosmolality, concomitant treatment with antihypertensive medications or CNS depressants, patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. LYLBALVI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

**Fails:** Antipsychotics, including LYLBALVI, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including LYLBALVI. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of LYLBALVI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue LYLBALVI in patients with severe neutropenia (absolute neutrophil count <1000/μL) and follow their WBC until recovery.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic use. Antipsychotic drugs, including LYLBALVI, should be used cautiously in patients at risk for aspiration.

**Seizures:** Like other antipsychotic drugs, LYLBALVI may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

**Potential for Cognitive and Motor Impairment:** LYLBALVI, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, or motor skills. In a LYLBALVI placebo-controlled study, somnolence occurred in 9% of LYLBALVI-treated patients compared to 2.2% in patients treated with placebo.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that LYLBALVI therapy does not affect them adversely.

**Body Temperature Dysregulation:** Atypical antipsychotics may disrupt the body’s ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use LYLBALVI with caution in patients who may experience these conditions.

**Anticholinergic (Antimuscarinic) Effects:** Olanzapine, a component of LYLBALVI, exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with oral olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations, but LYLBALVI should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant propranolol hypertrophy, constipation, or a history of paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D₂ receptors, olanzapine, a component of LYLBALVI, elevates prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impeding gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

In the 4-week placebo-controlled trial, shifts from normal to high prolactin values (>30 ng/mL for females; >20 ng/mL for males) occurred in 41.4% of females and 32.9% of males treated with LYLBALVI, in 56.1% of females and 37.1% of males treated with olanzapine, and in 10% of females and 4.8% of males treated with placebo.

In the 24-week, olanzapine-controlled study, shifts from normal to high prolactin values occurred in 32.9% of females and 22.5% of males treated with LYLBALVI, and in 41.7% of females and 28.5% of males treated with olanzapine.

**Risks Associated with Combination Treatment with Lithium or Valproate:** If LYLBALVI is administered with lithium or valproate, refer to the lithium or valproate prescribing information for a description of the risks for these products including, but not limited to, the warnings and precautions for lithium or valproate.

**ADVERSE REACTIONS**

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

**Adverse Reactions in Patients with Schizophrenia:**

**Patient Exposure**

The safety of LYLBALVI was evaluated in 1262 patients (18 to 67 years of age) diagnosed with schizophrenia in four double-blind, controlled studies and three long-term safety extension studies of up to 3 years of duration. This experience corresponds to approximately 910 person-years. In these studies, there were a total of 663 patients exposed to LYLBALVI for at least 6 months, and 386 patients for at least one year.

**Adverse Reactions in the Short-Term (4 week) Placebo-Controlled Trial in Adults with Schizophrenia**

The most common adverse reactions (incidence of at least 5% of patients exposed to LYLBALVI and greater than twice the rate of placebo) are weight increased, somnolence, dry mouth, and headache. Adverse reactions associated with the use of LYLBALVI (incidence of 2% or greater and greater than in placebo-treated patients) are shown in Table 1.

### Table 1: Adverse Reactions Reported in ≥2% of LYLBALVI-Treated Patients and Greater than Placebo in a 4-Week Schizophrenia Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=134) %</th>
<th>LYLBALVI (10 mg/10 mg, 20 mg/10 mg) (N=134) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increased</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Blood insulin increased</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Adverse reactions that led to discontinuation in LYLBALVI-treated patients in the short-term placebo-controlled trial in adults with schizophrenia include schizophrenia (1%) and abnormal liver function tests (1%).

**Adverse Reactions in the Long-Term (24-week), Active-Controlled Trial in Adults with Schizophrenia**

In the 24-week, olanzapine-controlled trial in patients with stable schizophrenia, adverse reactions associated with the use of LYLBALVI (incidence of 2% or greater) include: weight increased (25%), somnolence (21%), dry mouth (13%), increased appetite (11%), waist circumference increased (6%), blood creatine phosphokinase increased (5%), headache (4%), lethargy (4%), sedation (4%), akathisia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), constipation (3%), dizziness (3%), fatigue (3%), nausea (3%), blood pressure increased (3%), neutrophil count decreased (3%), blood insulin increased (2%), weight decreased (2%), and dyslipidemia (2%).

Adverse reactions that led to LYLBALVI treatment discontinuation in more than one patient include somnolence (2%), weight increased (2%), neuroleptic malignant syndrome (2%), glycosylated hemoglobin increased (1%), schizophrenia (1%), and liver function test abnormal (1%).

**Hyperglycemia:** Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of
Table 2: Changes in Glycemic Parameters in a 24-Week Trial of Patients with Schizophrenia

<table>
<thead>
<tr>
<th>Glycemic Parameter</th>
<th>LYBALVI</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>12 (26/223)</td>
<td>8 (18/219)</td>
</tr>
<tr>
<td>Impaired (≥100 mg/dL and &lt;126 mg/dL) to High (≥126 mg/dL)</td>
<td>24 (9/38)</td>
<td>11 (5/47)</td>
</tr>
<tr>
<td>Increase ≥10 mg/dL</td>
<td>66 (174/265)</td>
<td>57 (154/270)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≤5.7%) to Impaired (≥5.7% and &lt;8.5%)</td>
<td>42 (68/204)</td>
<td>35 (68/197)</td>
</tr>
<tr>
<td>Normal to High (≤5.7% to ≥8.5%)</td>
<td>0.5 (1/204)</td>
<td>1.5 (3/197)</td>
</tr>
<tr>
<td>Impaired (≥5.7% and &lt;8.5%) to High (≥8.5%)</td>
<td>9.5 (6/63)</td>
<td>9.2 (17/76)</td>
</tr>
</tbody>
</table>

* n: number of patients with reported abnormal shifts; N: number of patients who had assessments at both baseline and endpoint for mean change, or normal at baseline and at least 1 post-baseline assessment for shift.

Drug Interactions

**DRUG INTERACTIONS**

**Effects of Other Drugs on LYBALVI:** Table 3 describes clinically significant drug interactions where the concomitant use of other drugs affects LYBALVI.
LYBALVI, during pregnancy. Healthcare providers are encouraged to register patients who may be less effective or ineffective shortly after LYBALVI discontinuation because LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are undergoing acute opioid withdrawal.

**Opioids:** LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. In emergency situations, if a LYBALVI-treated patient requires opioid treatment for anesthesia or analgesia, discontinue LYBALVI. The opioid should be administered by properly trained individual(s), and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

In non-emergency situations, if a LYBALVI-treated patient is expected to require opioid treatment (e.g., for analgesia during or after an elective surgical procedure) discontinue LYBALVI at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed. Given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after LYBALVI discontinuation because of the presence of samidorphan.

**Use in Specific Populations**

**Pregnancy**

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including LYBALVI, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2368 or visit https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

Risk Summary: Neonates exposed to antipsychotic drugs, including the olanzapine component of LYBALVI, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Overall, published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available data on the use of samidorphan or the combination of olanzapine and samidorphan in pregnant women to determine a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There is risk to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including LYBALVI, during pregnancy.

**Lybalvi**

In an animal reproduction study, oral administration of olanzapine and samidorphan to pregnant rats during the period of organogenesis produced adverse effects on embryofetal development and fetal toxicity at maternally toxic doses that are 6 times and >400 times the maximum recommended human dose (MRHD) of 20 mg/10 mg olanzapine/samidorphan in LYBALVI, respectively based on AUC. There were no adverse effects on embryofetal development at doses of olanzapine and samidorphan that are approximately 1 and 80 times, respectively, the MRHD based on AUC.

**Olanzapine**

In animal reproduction studies, there was no evidence of malformations in rats or rabbits when orally administered olanzapine at doses up to 9 and 30 times the MRHD dose (20 mg) based on mg/m² body surface area, respectively. In an oral rat embryofetal developmental toxicity study, early resorptions and increased numbers of nonviable fetuses were observed at a dose 9 times the MRHD based on mg/m² body surface area and gestation was prolonged at 5 times the MRHD based on mg/m² body surface area. In an oral rabbit embryofetal developmental toxicity study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of olanzapine which is 30 times the MRHD based on mg/m² body surface area.

**Samidorphan**

In animal reproduction studies, oral administration of samidorphan to pregnant rats and rabbits during the period of organogenesis caused fetal toxicities in rats only at maternally toxic doses that are >248 times the human exposure at the MRHD of 10 mg/day based on AUC. Oral administration of samidorphan to pregnant rats during pregnancy and lactation resulted in lower pup survival and decreased pup weights at 188 times the human exposure at the MRHD based on AUC.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

**Clinical Considerations**

**Disease-Associated Maternal and/or Embryofetal Risk**

There is risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

**Fetal/Neonatal Risks**

**Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including the olanzapine component of LYBALVI, during the third trimester of pregnancy.**

These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

**Data**

Human Data: Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

**Animal Data**

Olanzapine and samidorphan were orally administered to pregnant rats during the period of organogenesis at doses of 0.5/10, 2.5/50, 6/200, and 0/200 mg/kg/day (olanzapine/samidorphan) which are approximately <1/10 times to 6/4/6 times the MRHD of 20 mg/10 mg olanzapine/samidorphan, respectively, based on AUC. Maternal toxicity consisting of decreased body weight and food consumption was observed at all dose levels. Administration of samidorphan alone (200 mg/kg/day) and 6/200 mg/kg/day olanzapine/samidorphan decreased mean fetal body weights, increased litter incidence of bent ribs and bent scapula, however, the incidence of bent scapula and bent ribs was not increased when samidorphan was administered in combination with olanzapine compared to the incidence with samidorphan alone. Administration of olanzapine/samidorphan at 6/200 mg/kg/day also increased resorptions and post-implantation loss, with correlating lower mean viable fetuses and litter size. The no observed adverse effect level (NOAEL) for embryofetal development is 2/50 mg/kg/day, which is approximately 1/80 times the MRHD of 20 mg/10 mg olanzapine/samidorphan respectively, based on AUC.

**Table 3: Effects of Other Drugs on LYBALVI (cont’d)**

<table>
<thead>
<tr>
<th>Prevention/Management</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYBALVI may enhance the effects of certain antihypertensive agents.</td>
<td>Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.</td>
</tr>
</tbody>
</table>

**Table 4: Effects of LYBALVI on Other Drugs**

**Antihypertensive Agents**

**Clinical Implication:** LYBALVI may enhance the effects of certain antihypertensive agents.

**Prevention/Management:** Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

**Levodopa and Dopamine Agonists**

**Clinical Implication:** LYBALVI may antagonize the effects of levodopa and dopamine agonists.

**Prevention/Management:** Concomitant use of LYBALVI is not recommended with levodopa and dopamine agonists.
Olanzapine
Olanzapine was orally administered to pregnant rats and rabbits during the period of organogenesis at doses up to 18 mg/kg/day in rabbits and at doses up to 30 mg/kg/day in rats and at doses up to 3 mg/kg/day in dogs. No evidence of malformations was observed in an oral rat embryofetal developmental toxicity study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD based on mg/m² body surface area), and skeletal malformations occurred at a maternal dose of 18 mg/kg/day (9 times the MRHD based on mg/m² body surface area). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD based on mg/m² body surface area) in an oral rabbit embryofetal developmental toxicity study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternal dose of 30 mg/kg/day (30 times the MRHD based on mg/m² body surface area).

In an animal reproduction study, oral administration of samidorphan to pregnant rats during the period of organogenesis produced bent ribs and bent sternebrae; however, the incidence of bent sternebrae and bent ribs at maternally toxic doses of ≥100 mg/kg/day, and skeletal malformations (bent or misshapen forelimbs, hindlimbs, and/or scapula) at 300 mg/kg/day which are ~245 and 742 times the MRHD based on AUC, respectively, the NOAEL for embryofetal development is 25 mg/kg/day, which is approximately 29 times the MRHD based on AUC.

Samidorphan was orally administered to pregnant rats during the period of organogenesis at doses of 25, 100, and 300 mg/kg/day, which are approximately 29 to 742 times the MRHD of 10 mg/day based on AUC. Samidorphan was associated with an increased incidence of skeletal variations (unossified sternebrae and bent ribs) at maternally toxic doses of ≥100 mg/kg/day, and skeletal malformations (bent or misshapen forelimbs, hindlimbs, and/or scapula) at 300 mg/kg/day which are ~245 and 742 times the MRHD based on AUC, respectively. The NOAEL for embryofetal development is 25 mg/kg/day, which is approximately 29 times the MRHD based on AUC.

Samidorphan did not cause adverse effects on embryofetal development when orally administered to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 90 mg/kg/day, which are up to approximately 143 times the MRHD based on AUC.

Samidorphan was orally administered to pregnant rats during pregnancy and lactation at doses of 10, 30, or 100 mg/kg/day, which are approximately 7 to 188 times the MRHD based on AUC. Reduced pup survival, lower birth weights, and decreased pup body weight gains were observed at 100 mg/kg/day, which is 188 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 36 times the MRHD based on AUC. There were no adverse effects on pup developmental landmarks, learning, memory, reflexes, or fertility.

Lactation
Risk Summary: Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extra-pyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There is no information on the effects of olanzapine on milk production. There are no data on the presence of samidorphan or the combination of olanzapine and samidorphan in human milk, the effects on the breastfed infant or the effects on milk production. When samidorphan was administered to lactating rats, samidorphan and a metabolite were detected in the plasma of nursing pups, likely due to the presence of samidorphan in milk. Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extra-pyramidal symptoms (tremors and abnormal muscle movements). The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for LYBALVI and any potential adverse effects on the breastfed infant from LYBALVI or from the underlying maternal condition.

Females and Males of Reproductive Potential
Infertility
Female
Based on the pharmacologic action of olanzapine (D2 antagonist), treatment with LYBALVI may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

Pediatric Use: The safety and effectiveness of LYBALVI have not been established in pediatric patients.

Geriatric Use: Clinical studies of LYBALVI did not include sufficient numbers of patients 65 years of age and older to determine whether they responded differently than younger adult patients.

Olanzapine: Of the 2,500 patients in premarketing clinical studies with orally administered olanzapine, 11% (263) were 65 years of age or over. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo.

In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine, compared to patients treated with placebo.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1,184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than in placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthma, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than with placebo (13% vs 7%).

Consider a lower dosage of the olanzapine component of LYBALVI in geriatric patients who may have decreased clearance or an exaggerated pharmacodynamic response to olanzapine (e.g., oversedation).

Hepatic Impairment: Olanzapine and samidorphan plasma exposures were found to be higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. The effect of severe hepatic impairment was not studied. The higher plasma exposure in patients with moderate hepatic impairment was not expected to be clinically relevant. No dose adjustment of LYBALVI is needed in patients with hepatic impairment.

Renal Impairment: Plasma exposure to olanzapine and samidorphan was higher in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²) compared to those with normal renal function. No dose adjustment of LYBALVI is needed in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²), or severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²).

The effect of LYBALVI in patients with end-stage renal disorder was not studied. LYBALVI is not recommended for patients with end-stage renal disorder (eGFR of <15 mL/minute/1.73 m²).

OVERDOSAGE
Human Experience: There is limited clinical experience with overdose with LYBALVI. In premarketing clinical trials of LYBALVI involving 861 patients, overdose of LYBALVI was identified in 7 patients. This included 4 patients with accidental overdose, 2 with intentional overdose, and 1 due to a medication administration error. None of the reported overdoses was associated with a fatal outcome. There was a reported ingestion of 11 tablets of LYBALVI 10 mg/10 mg (5.5 times and 11 times the maximum recommended daily dosage of the olanzapine and samidorphan components of LYBALVI, respectively). The patient was found unresponsive and admitted to the hospital. Medical treatment included fluids, electrolytes, a diuretic, and a detoxicant; the patient stabilized within 2 days.

In postmarketing reports of overdose with olanzapine, a component of LYBALVI, symptoms included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Less commonly reported symptoms include: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neurologic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2,000 mg.

Management of Overdose: No specific antidotes for LYBALVI are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a certified Poison Control Center (1-800-222-1222) for additional overdosage management recommendations.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide). This Brief Summary is based on LYBALVI full Prescribing Information (revised: May 2021).

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