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**

**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 toevinacumab-dgnb 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](https://www.evkeezahcp.com) to learn more about EVKEEZA
EVKEEZA® lowered LDL-C by ~50%, on average, at 24 weeks

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 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%.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: -172 to -92; P<0.001).1,2

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; DBT=double-blind treatment period; IV=intravenous; non-HDL-C=non-high-density lipoprotein-cholesterol; PCSK9=proprotein convertase subtilisin kexin type 9; SE=standard error.

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 (≥2%) 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.

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 with EVKEEZA 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.

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


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777 Old Saw Mill River Road, Tarrytown, NY 10591

EVK.21.08.0002
08/2021
EVKEEZA (evinacumab-dgnb) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
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 familial hypercholesterolemia (HoFH).
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined.

4 CONTRAINdications
EVKEEZA is contraindicated in patients with a history of serious hypersensitivity reaction to evinacumab-dgnb or to any of the excipients in EVKEEZA.

5 WARNINGS AND PREcautions
5.1 Serious Hypersensitivity Reactions
Serious hypersensitivity reactions have occurred with EVKEEZA. In clinical trials, 1 (1%) EVKEEZA-treated patient experienced anaphylaxis versus 0 (0%) patients who received placebo. If signs or symptoms of serious hypersensitivity reactions occur, discontinue EVKEEZA infusion, treat according to the standard-of-care, and monitor until signs and symptoms resolve. EVKEEZA 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, EVKEEZA 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 EVKEEZA. Advise patients who may become pregnant to use effective contraception during treatment with EVKEEZA and for at least 5 months following the last dose of EVKEEZA [see Use in Specific Populations (8.1)].

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 EVKEEZA. The mean age of EVKEEZA-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-four (54%) EVKEEZA-treated patients had HoFH. Patients received EVKEEZA as add-on therapy to other lipid-lowering therapies, including maximally tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and apheresis.

Adverse reactions that occurred during EVKEEZA treatment are listed in Table 1. The most common adverse reactions (in greater than 3% of EVKEEZA-treated patients and more frequently than in placebo) are shown in Table 1. Other adverse reactions occurring in less than 3% of patients treated with EVKEEZA 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 EVKEEZA infusion but did not require intervention and resolved post-infusion.

Serious Hypersensitivity Reactions
Anaphylaxis was reported in 1 (1%) patient treated with EVKEEZA and 0% in patients who received placebo.

Infusion Reactions
Infusion reactions were reported in 6 (7%) patients treated with EVKEEZA and in 2 (4%) patients who received placebo. The following infusion reactions occurred in EVKEEZA-treated patients during clinical trials: pyrexia, pruritus, rash, respiratory symptoms, exacerbation of angioedema, and ventricular tachycardia.

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of any antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in clinical trials may underestimate or overestimate the true incidence of antibody formation in clinical practice. The presence of antibodies to a therapeutic protein may reduce the therapeutic effect of the protein and/or increase the risk of an adverse reaction. The safety and effectiveness of EVKEEZA have not been established in pediatric patients with HoFH who are younger than 12 years old.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy
Based on data from animal reproduction studies, EVKEEZA 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 IgG4 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, hypogonsalia, 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 for major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, 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 EVKEEZA, healthcare providers should report EVKEEZA exposure by calling 1-833-385-3392.

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 exposure and linear 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 EVKEEZA and any potential adverse effects on the breastfed infant from EVKEEZA or the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Consider pregnancy testing in patients who may become pregnant prior to starting treatment with EVKEEZA [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)].

Contraception
Females
Based on animal studies, EVKEEZA 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 EVKEEZA and for at least 5 months following the last dose of EVKEEZA.

8.4 Pediatric Use

Pediatric Use
Clinical studies of EVKEEZA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.
The growth in enrollment in Medicare Advantage (MA) plans has been attracting a lot of attention lately. Close to half of Medicare beneficiaries have opted for an MA plan, and the Congressional Budget Office has projected that the upswing will continue so that by 2030, more than half of Medicare beneficiaries will be in MA plans. Experts debate the whys and wherefores of the migration to MA, but there is no denying that Medicare is increasingly becoming healthcare coverage that is publicly funded but privately managed.

The same thing has been going on in the Medicaid program for decades — and almost under the radar. That’s partly because Medicaid is a decentralized program that varies on a state-by-state basis. Starting in the 1980s, states started to contract out the management of the Medicaid programs. One major difference between MA and Medicaid managed care is that the decision to enroll in MA lies with the beneficiaries. With Medicaid managed care, it is state-level Medicaid officials who have made the decision. As Joseph Burns reports in our cover story, they saw the advantage of healthcare that was managed for state employees and so applied it to people covered by their Medicaid programs. Now more than two-thirds of the people covered by Medicaid have their healthcare managed by private businesses that have negotiated contracts with state Medicaid programs.

The logic of managing the care of those with Medicaid coverage is overwhelming. Complex and costly health conditions accrue in Medicare populations because of the social determinants of health. Medicaid managed care has helped make Medicaid a more predictable expense for state officials. But as our cover story reports, a number of state officials are now beginning to look under the hood of their Medicaid contracts, particularly at how pharmacy benefits have been managed. Without getting into the merits of the individual investigations, it is a healthy development that questions are being asked. It is also a positive development that the federal Centers for Medicare and Medicaid Services is stepping up its oversight and that plans will be required to file annual reports.

For Medicaid managed care to live up its promise, it can’t be a blank check.
Francois de Brantes, M.S., MBA, is senior vice president of commercial business development at Signify Health.

Otis Brawley, M.D., is a Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University and former chief medical and scientific officer of the American Cancer Society.

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Lili Brillstein is a nationally recognized thought leader in the advancement of Episodes of Care as a value-based approach for specialty care. She is the CEO of BCollaborative, which works with stakeholders across the healthcare continuum to successfully make the move from fee for service to value-based healthcare.

David Calabrese, RPh, MHP, is market president, Health Plans/PBMs at OptumRx, a pharmacy benefits firm that provides services for more than 65 million lives nationally.

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Kevin Ronneberg, M.D., is vice president and associate medical director for health initiatives at HealthPartners, an integrated, nonprofit provider and health insurance company located in Bloomington, Minnesota.

Marc Samuels, J.D., M.P.H., is the CEO of ADVI, a strategic advisory services life sciences firm in Washington, D.C.

William Shrank, M.D., is Humana’s senior vice president and chief medical officer. In this role, he is responsible for leading and implementing the company’s integrated care delivery strategy. This strategy emphasizes a consumer-friendly, evidence-based, technology-enabled approach to personalized health improvement for the company’s more than 16 million Humana health plan members.

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For adults at risk of rapid disease progression, TARPEYO: First and only treatment FDA approved to reduce proteinuria in IgA Nephropathy.

TARPEYO™ (budesonide) delayed release capsules is designed to deliver treatment to an area of the ileum to target mucosal B cells, which are responsible for the production of galactose-deficient IgA1 antibodies, causing immunoglobulin A Nephropathy (IgAN).

*Drug release is initiated in the ileum by the pH-dependent disintegration of the enteric coat.

**Indication**
TARPEYO™ (budesonide) delayed release capsules is a corticosteroid indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on a reduction in proteinuria. It has not been established whether TARPEYO slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

**Important Safety Information**

**Contraindications:** TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis, have occurred with other budesonide formulations.

**Warnings and Precautions**

**Hypercorticism and adrenal axis suppression:** When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy (see Dosing and Administration) or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

**Risks of immunosuppression:** Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressive doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection; untreated fungal, bacterial, systemic viral, or parasitic infections; or ocular herpes simplex. Avoid exposure to active, easily transmitted infections (eg, chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

**Risks of immunosuppression:** Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressive doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection; untreated fungal, bacterial, systemic viral, or parasitic infections; or ocular herpes simplex. Avoid exposure to active, easily transmitted infections (eg, chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.
Designed to deploy in the ileum²,³,⁴
- Designed to deliver treatment to the area of the ileum, where mucosal B cells are located
- Mucosal B cells express glucocorticoid receptors and produce galactose-deficient IgA1 antibodies, causing IgAN
- Through anti-inflammatory and immunosuppressive effects at the glucocorticoid receptor, TARPEYO can modulate B cell numbers and activity

Statistically significant reduction in UPCR with TARPEYO plus RASi vs RASi alone at 9 months¹,⁵
- **Primary endpoint:** Significant reduction (34%) in UPCR from baseline was achieved in the TARPEYO plus renin-angiotensin system inhibitor (RASi)-treated group (n=97) vs 5% with RASi alone (n=102) at 9 months¹,⁵
  - After 3 months of observational follow-up, a 53% reduction from baseline in UPCR was seen in the TARPEYO plus RASi-treated group (n=97) vs 9% with RASi alone (n=102)²,⁶

  Additional data presented beyond the primary endpoint of 9 months should be interpreted cautiously.

**eGFR data with TARPEYO plus RASI vs RASI alone at 9 months**
- **Secondary endpoint:** At 9 months, absolute change in eGFR was -0.6 mL/min/1.73 m² with TARPEYO plus RASI (n=97) vs -4.0 mL/min/1.73 m² with RASI alone (n=102)²,⁶

  These interim secondary endpoint data were not prospectively controlled for multiplicity and need cautious interpretation. The clinical significance of these results is unknown. Confirmatory clinical trial results are required to draw any conclusions. It has not been established whether TARPEYO has demonstrated a benefit in slowing kidney function decline in patients with IgAN.²

**Demonstrated safety profile**
- 87% of patients in the TARPEYO plus RASI-treated group reported adverse reactions vs 73% of patients on RASI alone²,³
- In clinical studies, the most common adverse reactions of TARPEYO plus RASI (occurring in ≥10% of patients treated with TARPEYO plus RASI and at a higher incidence than RASI alone) were: hypertension, peripheral edema, muscle spasms, and acne²,³
- Incidence of serious adverse events with TARPEYO plus RASI vs RASI alone (1.1% vs 8.3%)²
- Incidence of adverse events leading to treatment discontinuation of TARPEYO plus RASI vs RASI alone (9% vs 1%)²

  The safety profile is generally consistent with the well-established safety profile of the active ingredient, budesonide³

**Study Design:** NefiGard is an ongoing, phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of TARPEYO 16 mg/day vs placebo in patients with primary IgAN as an addition to optimized RAS blockade therapy. Part A of the study (n=199) included a 9-month blinded treatment period and a 3-month follow-up period. The primary endpoint was UPCR at 9 months; eGFR was a secondary endpoint.

Part B, a confirmatory validation study in which no treatment will be administered, will assess eGFR over 2 years.¹,³

¹It has not been established to what extent the efficacy of TARPEYO is mediated via local effects in the ileum vs systemic effects.¹
²[31% reduction (95% CI: 16%–42%) in UPCR with TARPEYO plus RASI vs RASI alone (P=0.001)]²,³
³All patients with a UPCR/eGFR reading regardless of use of prohibited medication at 9 months and 12 months.¹,³
⁴Adjusted geometric least squares mean ratio of UPCR relative to baseline were based on a longitudinal repeated measures model.¹
⁵49% reduction (95% CI, 37–58%) in UPCR with TARPEYO plus RASI vs RASI alone.²
⁶Absolute changes derived from geometric least square mean ratios using the pooled baseline geometric mean.²

**Warnings and Precautions (cont’d)**

**Other corticosteroid effects:** TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, a family history of diabetes or glaucoma, or with any other condition in which corticosteroids may have unwanted effects.

Adverse reactions: In clinical studies, the most common adverse reactions with TARPEYO (occurring in ≥5% of TARPEYO patients and ≥3% higher than placebo) were: hypertension (16%), peripheral edema (14%), muscle spasms (13%), acne (11%), dermatitis (7%), weight increase (7%), dyspepsia (6%), face edema (6%), dyspepsia (5%), fatigue (5%), and hirsutism (5%).

**Drug interactions:** Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and ciclosporine. Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide.

**Use in specific populations**

**Pregnancy:** The available data from published case series, epidemiological studies, and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgAN. Infant exposure to in utero corticosteroids, including budesonide, are at risk for hypothalamus.

**Please see brief summary of Full Prescribing Information on the adjacent pages.**

**References:**
1. TARPEYO. Prescribing Information. Calliditas Therapeutics AB. 2021

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Learn more about how TARPEYO works at TARPEYOhcp.com
TARPEYO™ (budesonide) delayed release capsules
Brief Summary of Prescribing Information

4 CONTRAINDICATIONS
TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression
When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy (see Dosing and Administration [2]) or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

5.2 Risks of Immunosuppression
Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3 Other Corticosteroid Effects
TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

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

- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.1)]
- Risks of immunosuppression [see Warnings and Precautions (5.2)]
- Other corticosteroid effects [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 safety of TARPEYO has been evaluated in a randomized controlled study in 197 patients. The most common adverse reactions reported in greater than or equal to 5% of TARPEYO-treated patients are listed in Table 1. The majority of adverse reactions were mild or moderate in severity.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of TARPEYO-treated patients, and greater than or equal to 2% higher than Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TARPEYO 24 mg (N=97)</th>
<th>Placebo (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Patients with any Adverse Reaction</td>
<td>84 (87)</td>
<td>73 (78)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (13)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>14 (14)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>14 (14)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Acne</td>
<td>11 (11)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>7 (7)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>7 (7)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hiccough</td>
<td>5 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Most adverse reactions that occurred at a greater incidence for TARPEYO compared to placebo were consistent with hypercortisolsim.

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 Inhibitors
Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine. Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism (see Clinical Considerations). In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during
organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels (see Data). The estimated background risk of major birth defects and miscarriage of the indicated population 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 Embryo/Fetal Risk IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight. Fetal/Neonatal Adverse Reactions Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly (see Warnings and Precautions [5.1]).

Data Animal Data Budesonide was teratogenic and embryo-lethal in rabbits and rats. In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).

Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis). In a peri- and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures ≥ 0.012 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation
Risk Summary Breastfeeding is not expected to result in significant exposure of the infant to TARPEYO. Lactation studies have not been conducted with oral budesonide, including TARPEYO, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide (see Data). Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TARPEYO and any potential adverse effects on the breastfed infant from TARPEYO, or from the underlying maternal condition.

Data One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide. Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5-kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg TARPEYO. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.4 Pediatric Use
The safety and efficacy of TARPEYO in pediatric patients have not been established.

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

8.6 Hepatic Impairment
Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide (see Warnings and Precautions [5.1] and Clinical Pharmacology [12.3]). Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

10 OVERDOSAGE
Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

Please see Full Prescribing Information for TARPEYO at TARPEYOhcp.com TARPEYO is a registered trademark of Calliditas Therapeutics AB, or its affiliates. © Calliditas Therapeutics AB All rights reserved. 4/22 US-NEF-2100006-A
WELLBEING CHECKUP

Ergonomics

The stress on the back and neck muscles that come with being a surgeon can have long-term effects. Inder Paul Singh, M.D., an ophthalmologist in southeastern Wisconsin, discusses steps that physicians can take to improve the ergonomics of their work.

https://www.medicalworldnews.com/view/wellbeing-checkup-ergonomics

AFTER HOURS

Mountain Climbing

Growing up in Utah, Christopher Weight, M.D., a urologist at Cleveland Clinic, became interested in climbing at an early age. He has climbed mountains such as Devil’s Tower in Wyoming and the Matterhorn in the Alps. Weight spoke about climbing for kidney cancer awareness through his involvement with the Climb 4 Kidney Cancer organization.

https://www.medicalworldnews.com/view/after-hours-mountain-climbing

SECOND OPINION

A Prostate Cancer Case

Judd W. Moul, M.D., a urologic oncologist at the Duke Cancer Center in Durham, North Carolina, and a member of Oncology® editorial board, discusses a recent case with Duke medical student Kostantinos E. Morris. The case involved a patient who presented at their clinic with elevated prostate-specific antigen (PSA) levels but multiple imaging tests that appeared to indicate the absence of malignancy. Moul and Morris discuss how they continued to investigate the cause of the elevated PSA levels and overcame the patient’s reluctance for further testing — and the ultimate outcome.

https://www.medicalworldnews.com/view/second-opinion-prostate-cancer-case
"Paxlovid rebound is real and poorly understood," tweeted Bob Wachter, M.D., on May 11. "We need urgent study & pt counseling."

Wachter’s tweet came as word about possible Paxlovid rebound started to ricochet around social media and conventional media outlets. Wachter, a professor and chair of the Department of Medicine at the University of California, San Francisco, has emerged as one of the leading social media voices on the COVID-19 pandemic.

Paxlovid rebound refers to the phenomenon of symptomatic COVID-19 coming back a few days after people have finished taking the prescribed five-day course of Pfizer’s oral antiviral medication and test negative. No one is sure why it occurs or exactly how often.

FDA officials have acknowledged the problem. In an interview transcript posted on the FDA website in early May, John Farley, M.D., M.P.H., director of the Office of Infectious Diseases in the agency’s Center for Drug Evaluation and Research, discussed the clinical trial that supported the agency’s decision to issue an emergency use authorization (EUA) for Paxlovid. Between 1% and 2% of study participants had one or more positive polymerase chain reaction (PCR) tests for the SARS-CoV-2 virus, which causes COVID-19, after testing negative or a test result showing an increase in the amount of SARS-CoV-2. Farley noted, though, the same was true for those assigned to the placebo group, so the rebound couldn’t necessarily be attributed to Paxlovid.

The CDC chimed in at the end of May with an advisory that acknowledged the case reports. But the advisory also noted that the cases of rebound illness were mild. Farley and others have noted the benefits of Paxlovid. The trial that led to the EUA showed the antiviral reduced the risk of hospitalization or death by 88% among nonhospitalized patients at high risk of developing a severe case of COVID-19. However, people enrolled in that trial were not vaccinated. The news of Paxlovid rebound has stirred up questions about whether the antiviral might have a different effect on people who have been vaccinated.

Paxlovid consists of nirmatrelvir, which acts directly on the SARS-CoV-2 virus, and ritonavir, a repurposed HIV drug that boosts the effectiveness of nirmatrelvir. As a convenient oral drug with good efficacy data behind it, the antiviral has been heralded as a key weapon in the fight against COVID-19.

One of the proposed explanations for Paxlovid rebound is that immune response to the virus is incomplete because the antiviral knocks down the viral load, so when the five days of treatment are over, the infection springs back. Paul E. Sax, M.D., clinical director of the Division of Infectious Diseases at Brigham and Women’s Hospital in Boston, has floated the idea that SARS-CoV-2 replication is drawn out in some people and that although Paxlovid reduces it, the replication ramps up again once the five-day course is over.

Paxlovid rebound has raised questions about how long people with COVID-19 who have taken the antiviral should isolate. Also unsettled is whether a second-course of Paxlovid might be used to treat the rebound infection. Sax, writing in NEJM Journal Watch, said re-treatment is permitted under the EUA and is justified for high-risk patients, such as those who are severely immunocompromised. However, in the transcript posted on the FDA website, Farley said there was no evidence of benefit from longer or repeated treatment with Paxlovid. The CDC advisory also says there is no evidence of benefit from additional treatment.  

—Peter Wehrwein
Myfembree®
(relugolix, estradiol, and norethindrone acetate) tablets
40 mg, 1 mg, 0.5 mg

One small pill. Once a day.
The only FDA-approved once-daily pill to reduce heavy menstrual bleeding associated with uterine fibroids in premenopausal women

The recommended total duration of treatment is 24 months.¹
Pill size: 7.94 mm in diameter.

INDICATION
Myfembree is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Limitations of Use: Use of Myfembree should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS
- Estrogen and progestin combination products, including Myfembree, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events.
- Myfembree is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.

CONTRAINDICATIONS
Myfembree is contraindicated in women with any of the following; high risk of arterial, venous thrombotic, or thromboembolic disorder; pregnancy; known osteoporosis; current or history of breast cancer or other hormone-sensitive malignancies; known hepatic impairment or disease; undiagnosed abnormal uterine bleeding; known hypersensitivity to components of Myfembree.

WARNINGS AND PRECAUTIONS
Thromboembolic Disorders: Discontinue immediately if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs or is suspected. Discontinue at least 4 to 6 weeks before surgery associated with an increased risk of thromboembolism, or during periods of prolonged immobilization, if feasible. Discontinue immediately if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis as these have been reported with estrogens and progestins.

Bone Loss: Myfembree may cause a decrease in bone mineral density (BMD) in some patients, which may be greater with increasing duration of use and may not be completely reversible after stopping treatment. Consider the benefits and risks in patients with a history of low trauma fracture or risk factors for osteoporosis or bone loss, including medications that may decrease BMD. Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and periodically thereafter. Consider discontinuing Myfembree if the risk of bone loss exceeds the potential benefit.

Hormone-Sensitive Malignancies: Discontinue Myfembree if a hormone-sensitive malignancy is diagnosed. Surveillance measures in accordance with standard of care, such as breast examinations and mammography are recommended. Use of estrogen alone or estrogen plus progestin has resulted in abnormal mammograms requiring further evaluation.

Depression, Mood Disorders, and Suicidal Ideation: Promptly evaluate patients with mood changes and depressive symptoms including shortly after initiating treatment, to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior and reevaluate the benefits and risks of continuing Myfembree.

Hepatic Impairment and Transaminase Elevations: Steroid hormones may be poorly metabolized in these patients. Instruct women to promptly seek medical attention for symptoms or signs that may reflect liver injury, such as jaundice or right upper abdominal pain. Acute liver test abnormalities may necessitate the discontinuation of Myfembree use until the liver tests return to normal and Myfembree causation has been excluded.

Response rates with Myfembree
~70%

72.1% and 71.2% in LIBERTY 1 and 2 vs 16.8% and 14.7% for placebo, respectively (P<0.0001)²

• Myfembree was studied in LIBERTY 1 and 2, which were 2 replicate, 24-week, randomized, double-blind, placebo-controlled clinical trials that enrolled premenopausal women with heavy menstrual bleeding associated with uterine fibroids.³
• Response rate was the primary endpoint, defined as the proportion of women receiving Myfembree who achieved menstrual blood loss volume <80 mL and ≥50% reduction in menstrual blood loss volume from baseline over the last 35 days of treatment. Mean menstrual blood loss volume (± standard deviation) at baseline was 231 mL (± 156) ¹
Suspected. Discontinue at least 4 to 6 weeks before surgery associated with uterine bleeding; known hypersensitivity to components of Myfembree. Malignancies; known hepatic impairment or disease; undiagnosed abnormal increase the risk of thrombotic or thromboembolic disorders including Estrogen and progestin combination products, including Myfembree, increase the risk of thrombotic or thromboembolic disorders including. Myfembree is contraindicated in women with any of the following: high risk of High Blood Pressure: In patients with uncontrolled hypertension, monitor blood pressure and stop Myfembree if blood pressure rises significantly. Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing Myfembree. Avoid concomitant use of hormonal contraceptives. Myfembree may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue Myfembree if pregnancy is confirmed. Risk of Early Pregnancy Loss: Myfembree can cause early pregnancy loss. Exclude pregnancy before initiating and advise women to use effective non-hormonal contraception. Uterine Fibroid Prolapse or Expulsion: Advise women with known or suspected submucosal uterine fibroids about the possibility of uterine fibroid prolapse or expulsion and instruct them to contact their physician if severe bleeding and/or cramping occurs. Alopecia: Alopecia, hair loss, and hair thinning were reported in phase 3 trials with Myfembree. Consider discontinuing Myfembree if hair loss becomes a concern. Whether the hair loss is reversible is unknown. Effects on Carbohydrate and Lipid Metabolism: More frequent monitoring in Myfembree-treated women with prediabetes and diabetes may be necessary. Myfembree may decrease glucose tolerance and result in increased blood glucose concentrations. Monitor lipid levels and consider discontinuing if hypercholesterolemia or hypertriglyceridemia worsens. Common adverse events and discontinuation rates vs placebo

- Discontinuation rates due to adverse events (3.9%) were similar to placebo (4.3%)
- The most common adverse events occurring at ≥3% and at a greater incidence than placebo were hot flush/hyperhidrosis/night sweats; abnormal uterine bleeding; alopecia; and decreased libido. These are not all the possible side effects of Myfembree.

Learn more at MyfembreeHCP.com

Gallbladder Disease or History of Cholestatic Jaundice: Discontinue Myfembree if signs or symptoms of gallbladder disease or jaundice occur. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease. Elevated Blood Pressure: For women with well-controlled hypertension, monitor blood pressure and stop Myfembree if blood pressure rises significantly.

Effect on Other Laboratory Results: Of Myfembree is associated with increases in total cholesterol and LDL-C. Effect on Other Laboratory Results: Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy. Use of estrogen and progestin combinations may raise serum concentrations of binding proteins (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce free thyroid or corticosteroid hormone levels. Use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, and coagulation factors.

Hypersensitivity Reactions: Immediately discontinue Myfembree if a hypersensitivity reaction occurs.

ADVERSE REACTIONS: Most common adverse reactions for Myfembree (incidence ≥3% and greater than placebo) were hot flush/hyperhidrosis/night sweats, abnormal uterine bleeding, alopecia, and decreased libido. These are not all the possible side effects of Myfembree.

DRUG INTERACTIONS: P-gp inhibitors: Avoid use of Myfembree with oral P-gp inhibitors. If use is unavoidable, take Myfembree first, separate dosing by at least 6 hours, and monitor patients for adverse reactions. Combined P-gp and Strong CYP3A Inducers: Avoid use of Myfembree with combined P-gp and strong CYP3A inducers.

LACTATION: Advise women not to breastfeed while taking Myfembree.

Please see Brief Summary of the full Prescribing Information including BOXED WARNING on the following pages.


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MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use

**1. INDICATIONS AND USAGE**

MYFEMBREE is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

**2. CONTRAINDICATIONS**

- Estrogen and progestin combination products, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis (DVT), stroke and myocardial infarction (MI), especially in women at increased risk for these events.

**3. WARNINGS AND PRECAUTIONS**

- MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke and women with uncontrolled hypertension.

**4. ADVERSE REACTIONS**

- Estrogen and progestin combination products, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis (DVT), stroke and myocardial infarction (MI), especially in women at increased risk for these events.

**5. LIMITATIONS OF USE**

- Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

**6. DURABILITY OF EFFECT**

- MYFEMBREE is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

**7. NURSING MOTHERS**

- Breastfeeding is not recommended in postmenopausal women treated with MYFEMBREE.

**8. EFFECT ON LABORATORY TESTS**

- MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke and women with uncontrolled hypertension.
The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Thromboembolic Disorders and Vascular Events
- Bone Loss
- Depression, Mood Disorders, and Suicidal Ideation
- Hepatic Impairment and Transaminase Elevation
- Hypersensitivity Reactions

6.1 Clinical Trials Experience

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

The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study L1 (LIBERTY 1) and Study L2 (LIBERTY 2), in women with heavy menstrual bleeding associated with uterine fibroids. In the Phase 3 studies, women received one daily oral tablet plus an over encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix+E2/NETA), which is equivalent to 1 tablet of MYFEMBREE. Across the two studies, 254 women received MYFEMBREE once daily for 24 weeks. Additionally, 256 women received placebo for 24 weeks, and 258 women received relugolix 40 mg monotherapy once daily for 12 weeks followed by MYFEMBREE for 12 weeks.

In these, 476 women were treated with MYFEMBREE in a 28-week extension trial, Study L3 (LIBERTY Extension), for a total treatment duration of up to 12 months. Demographics were similar across the studies; approximately 43% were White, 51% were Black, and approximately 23% were of Hispanic or Latino ethnicity. The mean age at study entry was approximately 42 years (range 19 to 59 years).

Serious Adverse Reactions

Serious adverse reactions were reported in 3.1% of MYFEMBREE-treated women compared with 2.3% of placebo-treated women in Studies L1 and L2. In MYFEMBREE-treated women, serious adverse drug reactions included uterine myoma expulsion and menorrhagia experienced by one woman, uterine leiomyoma gyniopsis, cholecystitis, and pelvic pain reported for one woman each.

Adverse Reactions Leading to Study Drug Discontinuation

In the two placebo-controlled clinical trials (Study L1 and Study L2), 3.9% of women treated with MYFEMBREE discontinued therapy due to adverse reactions, compared with 4.2% receiving placebo. The most common adverse reaction leading to discontinuation of MYFEMBREE was uterine bleeding (1.2%) with onset usually reported within the first 3 months of therapy.

Common Adverse Reactions

The most common adverse reactions reported in at least 3% of women treated with MYFEMBREE and at an incidence greater than placebo during double-blind placebo-controlled treatment are summarized in Table 1.

### Table 1: Adverse Reactions Occurring in 3% or More of Women Treated with MYFEMBREE and at a Greater Incidence Than Placebo in Studies L1 and L2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MYFEMBREE (N = 254)</th>
<th>Placebo (N = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flush, hyperhidrosis, or night sweats</td>
<td>10.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>6.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>3.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Includes meningitis, endocarditis, sepsis, septicemia, empyema, pneumonitis, and myocardial infarct.

In one of the two Phase 3 clinical trials (Study L1), more women experienced the adverse reaction of new or worsening hypertension with MYFEMBREE compared as placebo (7.0% vs 0.8%).

Less Common Adverse Reactions

Adverse reactions occurring in at least 2% and less than 3% of women in MYFEMBREE group and greater incidence than placebo included irritability, dyspepsia, and breast cyst. Other important adverse reactions reported in women treated with MYFEMBREE included one serious reaction each of uterine myoma expulsion (0.4%) and uterine leiomyoma gyniopsis (0.4%).

The adverse reactions most commonly reported in the extension trial, Study L3, were similar to those in the placebo-controlled trials.

### Table 2: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Uterine Fibroids at Month 6 in Studies L1 and L2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N = 254)</th>
<th>MYFEMBREE (N = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>254</td>
<td>256</td>
</tr>
<tr>
<td>Percent Change from Baseline</td>
<td>-0.23 (95% CI: -0.62, 0.18)</td>
<td>-0.23 (95% CI: -0.64, 0.18)</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>-0.42</td>
<td></td>
</tr>
</tbody>
</table>

Includes those with and those without DXA scans at Month 6 and Month 12. MYFEMBREE is presented in Table 2. The effect of MYFEMBREE on BMD was assessed by dual-energy X-ray absorptiometry (DXA). The least squares mean percent change from baseline in lumbar spine BMD at Month 6 and Month 12 for women treated with MYFEMBREE in Studies L1 or L2 and then continued on MYFEMBREE for an additional 28 weeks was 28 weeks in Study L3 is presented in Table 2, below.

### Table 3: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD at Month 6 in Studies 1 and 2 and Month 12 in Study 3 in Women with Uterine Fibroids Treated with MYFEMBREE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N = 163)</th>
<th>MYFEMBREE (N = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>254</td>
<td>256</td>
</tr>
<tr>
<td>Percent Change from Baseline</td>
<td>-0.23 (95% CI: -0.62, 0.18)</td>
<td>-0.23 (95% CI: -0.64, 0.18)</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>-0.42</td>
<td></td>
</tr>
</tbody>
</table>

Includes those with and those without DXA scans at Month 6 and Month 12. MYFEMBREE is presented in Table 2. The effect of MYFEMBREE on BMD was assessed by dual-energy X-ray absorptiometry (DXA). The least squares mean percent change from baseline in lumbar spine BMD at Month 6 and Month 12 for women treated with MYFEMBREE in Studies L1 or L2 and then continued on MYFEMBREE for an additional 28 weeks was 28 weeks in Study L3 is presented in Table 2, below.

A separate concurrent prospective observational study enrolled 262 women with uterine fibroids who were age-matched to participants of Studies L1 and L2. These women did not receive treatment for uterine fibroids and underwent DXA scans at Month 6 and Month 12 to monitor for changes in BMD. Mean percent change from baseline (95% CI) in BMD at the lumbar spine at Month 6 and Month 12 was 0.00 (-0.32, 0.32) and -0.64 (-0.77, 0.05), respectively.

A decline in lumbar spine BMD of > 3% was observed in 4/209 (1.9%) women who had a DXA scan following 12 months of MYFEMBREE treatment in Study L3 and in 17.4% (37/213) of untreated women in the Observational Cohort. A decline of > 6% was seen in 1% (1/132) of women who treated a DXA scan at Month 12 and in 0.9% (2/213) of untreated women in the Observational Cohort.

In Studies L1, L2, and L3, 0.6% (4/634) women treated with MYFEMBREE experienced lost trauma fractures (defined as a fall from standing height or less). Two of these women were treated with relugolix monotherapy for 12 weeks prior to MYFEMBREE therapy.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of relugolix monotherapy outside of the United States. 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.

- Incomplete system disorders: anaphylactoid reaction
- Skin and subcutaneous tissue disorders: drug eruption, Neoplasms, benign, malignant and unspecified uterine leiomyoma degeneration
- Respiratory, thoracic and mediastinal disorders: pulmonary embolism

### 7 Drug Interactions

7.1 Effect of Other Drugs on MYFEMBREE

P-gp Inhibitors

Co-administration of MYFEMBREE with P-gp inhibitors increases the AUC and maximum concentration (Cmax) of relugolix, estradiol, and/or norethindrone and may decrease the therapeutic effects of MYFEMBREE. Avoid use of MYFEMBREE with oral P-gp inhibitors.

If use is unavoidable, take MYFEMBREE first, separate dosing by at least 6 hours, and monitor patients for adverse reactions.

### 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 MYFEMBREE during pregnancy. Pregnant females exposed to MYFEMBREE and healthcare providers are encouraged to call the MYFEMBREE Pregnancy Exposure Registry at 1-855-428-0707.

Risk Summary

MYFEMBREE is contraindicated in pregnancy. Based on findings from animal studies and its mechanism of action, MYFEMBREE may cause early pregnancy loss. Discontinue MYFEMBREE if pregnancy occurs during treatment.

The limited human data with the use of MYFEMBREE in pregnant women is insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes [see Data].

In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and fetal litter loss at all relugolix exposures about half that at the maximum recommended human dose (MRHD) of 40 mg. In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures above half and approximately 300 times exposures in women at the MRHD, [see Data].

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to estrogens and progesterones before conception or during early pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

In Study L1, L2, and L3, 0.6% (4/634) women treated with MYFEMBREE experienced lost trauma fractures (defined as a fall from standing height or less). Two of these women were treated with relugolix monotherapy for 12 weeks prior to MYFEMBREE therapy.
Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. No observed adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold lower than that in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD).

8.2 Lactation

Risk Summary

There are no data on the presence of relugolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix was detected in milk in lactating rats [see Data]. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.

Data

Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Based on animal data and the mechanism of action, MYFEMBREE can cause early pregnancy loss if MYFEMBREE is administered to pregnant women.

Pregnancy Testing

MYFEMBREE may delay the ability to recognize pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding. Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE and discontinue treatment if pregnancy is confirmed.

Contraception

Advise women of reproductive potential to use effective non-hormonal contraception during treatment with MYFEMBREE and for 1 week following discontinuation. Avoid concomitant use of hormonal contraceptives with MYFEMBREE. The use of estrogen-containing hormonal contraceptives may increase the risk of estrogen-associated adverse events and is expected to decrease the efficacy of MYFEMBREE.

8.4 Pediatric Use

Safety and effectiveness of MYFEMBREE in pediatric patients have not been established.

8.7 Hepatic Impairment

MYFEMBREE is contraindicated in women with hepatic impairment or disease. The use of E2 (a component of MYFEMBREE) in patients with hepatic impairment is expected to increase the exposure to E2 and increase the risk of E2-associated adverse reactions.

10. OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding. Supportive care is recommended if an overdose occurs. The amount of relugolix, estradiol, or norethindrone removed by hemodialysis is unknown.

Please see full Prescribing Information for Patient Counseling Information

This Brief Summary is based on MYFEMBREE Prescribing Information dated May 2021, which can be found at MYFEMBREE.com.

Manufactured by Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada.

Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005.

Approved: May 2021

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Asthma is a chronic respiratory disease that causes narrowing and inflammation of the airways that compromises breathing and, in some cases, can be fatal. Symptoms include coughing, wheezing, shortness of breath, chest tightness and chest pain. Nearly 25 million people in the United States have asthma, and 10 people die from the disease daily.

Current asthma treatment aims to prevent exacerbations (asthma attacks) and relieve symptoms when exacerbations occur. Traditional therapies include inhaled corticosteroids, long- and short-acting beta-agonist inhalers, long- and short-acting inhaled anticholinergics, leukotriene receptor antagonists and oral corticosteroids.

Most asthma cases are treatable using the currently available therapies mentioned. But about 10% of people with asthma do not respond to standard treatments and are considered to have severe asthma. The Global Initiative for Asthma (GINA) defines severe asthma as asthma that is not controlled by proper use of high-dose inhaled corticosteroids and long-acting beta-agonists or that worsens when high doses of these drugs are lowered.

Individuals with severe asthma often have persistent debilitating symptoms and require frequent use of inhalers and long-term use of oral corticosteroids. Although systemic corticosteroids can effectively treat asthma symptoms and exacerbations, their long-term use carries the risk of undesirable side effects, including osteoporosis and diabetes.

The good news is that research into the pathogenesis of asthma has led to the development of biologics that target cytokines directly involved in causing severe asthma symptoms. These cytokines include interleukin (IL)-4, IL-5 and IL-13, which are responsible for the high levels of eosinophils and immunoglobulin E (IgE) seen in some types of severe asthma.

Severe asthma is classified into three types based on patients’ response to treatment and the presence of certain biomarkers: allergic asthma, eosinophilic asthma, and noneosinophilic asthma.

Allergic asthma is triggered by exposure to allergens, such as pollen, dust and pet dander. Patients with this type of asthma typically have increased levels of IgE as a response to allergen exposure. People with eosinophilic asthma have high levels of eosinophils that trigger inflammation of the airways. Individuals who have noneosinophilic asthma have few if any eosinophils in lab results, although some may have high levels of neutrophils.

When it comes to treatment, patients with severe allergic or eosinophilic asthma tend to respond to inhaled corticosteroids and biologics that target biomarkers prevalent in these types of asthma. But inhaled corticosteroids are not effective for those with noneosinophilic asthma, and only one of the currently available biologics targets a cytokine active in this type of asthma.

**Approved biologics**

The past few years have seen a surge in the development and approval of biologics to treat severe asthma. Many of them target cytokines directly involved in the pathology of severe asthma, leading to reduced use of oral corticosteroids and significant decreases in severe exacerbations. As of 2021, GINA guidelines for the management of severe asthma include biologics as add-on therapy for severe allergic and eosinophilic asthma.

The biologics the FDA has approved as a treatment for severe asthma include Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), Tezspire (tezepelumab), and Xolair (omalizumab).

Xolair, developed by Swiss company Novartis, was the first biologic approved in the U.S. and the EU for children and adults with severe asthma. It is an anti-IgE monoclonal antibody for use in adults and children aged 6 and older with severe allergic asthma.

Fasenra, developed by Brit-
AstraZeneca is an IL-5 receptor antagonist. The FDA approved the drug in 2017 as add-on treatment for severe eosinophilic asthma in adults and children aged 12 and older. In 2019, the FDA approved the Fasenra Pen, a prefilled auto-injector for self-administration of the drug. GlaxoSmithKline’s Nucala and Teva Pharmaceutical’s Cinqair are IL-5 antagonists indicated as add-on therapy for eosinophilic asthma. Nucala, FDA-approved in 2015, is indicated for use in adults and children as young as 6 years. In January of this year, the FDA approved Nucala Autoinjector and prefilled syringes for self-administration for children, two and a half years after they were approved for adults. Cinqair, approved in the U.S. in 2016, is for intravenous use only in patients aged 18 and older.

Dupixent, coproduced by Regeneron Pharmaceuticals in upstate New York and French company Sanofi, received FDA approval in 2018 as add-on therapy for moderate to severe eosinophilic asthma in patients aged 12 and older. It had been previously approved as a treatment for eczema.

In October 2021, the FDA expanded Dupixent’s indication to include children aged 6 to 11 years. In 2020, the agency approved a Dupixent prefilled pen for self-injection. Dupixent is an IL-4 inhibitor with dual inhibitory action against IL-4 and IL-13 signaling.

Tezspire, produced by Amgen and AstraZeneca, is a first-in-class thymic stromal lymphopoietin (TSLP) blocker. TSLP is an epithelial cytokine responsible for starting a cascade of inflammation in asthma. Tezspire is the first agent with FDA-approved indications for all types of severe asthma, including noneosinophilic asthma, regardless of the presence of biomarkers. The agent was FDA approved in December 2021 as add-on treatment in patients aged 12 and older with severe asthma.

**Severe asthma pipeline**
Research continues to open new pathways in the treatment of severe asthma. Although biologics have done well in controlling severe eosinophilic and allergic asthma, a treatment need remains for patients with severe noneosinophilic asthma who do not respond to corticosteroids. Additionally, current biologics consist of injectable agents, many of which must be administered by a healthcare professional. A few companies are investigating new oral drugs and inhalers for use in patients with severe asthma.

**Masitinib**
Masitinib, from AB Science, a French company, is an oral tyrosine kinase inhibitor that selectively targets mast cells involved in mucus production and airway inflammation. In a phase 3 study, masitinib significantly reduced the rate of severe asthma exacerbations in patients with severe eosinophilic and noneosinophilic asthma compared with placebo.

**Depemokimab**
GlaxoSmithKline is conducting a phase 3 trial investigating the safety and efficacy of depemokimab as an add-on treatment in patients 12 years and older with severe eosinophilic asthma. Depemokimab, a long-acting IL-5 inhibitor, would become the first long-acting treatment for this condition if approved by the FDA. Current IL-5 inhibitors are dosed every 4 weeks or every 8 weeks. Depemokimab is designed to be administered every 6 months. The trial is scheduled to be finished in late 2023.

**Inhalers in the works**
AstraZeneca and British drug company Avillion are developing a combination inhaled short-acting beta-agonist (albuterol) and corticosteroid (budesonide) for use as rescue therapy. In a phase 3 trial, the albuterol/budesonide combination significantly reduced the risk of severe asthma exacerbations when used as rescue treatment versus albuterol alone in participants with moderate to severe asthma.

Ecleralimab is a TSLP inhibitor developed by Novartis as an inhaler for maintenance treatment of moderate to severe uncontrolled asthma. If approved, ecleralimab would join Tezspire as a treatment option for patients with all types of severe asthma. Ecleralimab is currently in a phase 2 study that is scheduled to be completed in 2024.

*Rosanna Sutherby, Pharm.D., is a medical writer and community pharmacist in High Point, North Carolina.*
Formulary Development

Aduhelm: Great expectations fizzle

Dogged by controversy, the new Alzheimer’s drug has not fared well since its approval by the FDA a year ago.

by DENISE MYSHKO

Before its approval on June 7, 2021, Aduhelm (aducanumab) was seen as possibly being one of the most important drugs launched in decades. It was heralded as the first new agent to treat Alzheimer’s disease in almost two decades. Moreover, data suggested it worked by reducing beta amyloid plaques in the brain, which many experts believe causes the disease.

At the time of its approval, some analysts projected that annual sales of Aduhelm could be between $8.2 billion and $10 billion. But now, a year after the FDA gave the drug an accelerated approval, those heady projections look like so many popped balloons. In 2021, Aduhelm generated just $3 million in sales, and in the first quarter of 2022, just $2.8 million. Biogen’s stock is trading at less than half the price it was in the days after the approval.

Biogen’s pricing strategy added fuel to the fire. The initial price tag for a year’s supply was $56,000. The Alzheimer’s Association, an important advocacy group to which Biogen has donated, called that price “simply unacceptable.” In December 2021, Biogen slashed the price in half. Still, the Institute for Clinical and Economic Review (ICER), an independent cost-effectiveness assessment organization in Boston, said Aduhelm would have to be priced far lower — between $3,000 and $8,000 — to meet typical cost-effectiveness thresholds.

Aduhelm got a cold reception by payers. Almost immediately after its approval, several Blue plans and the Department of Veterans Affairs indicated they wouldn’t cover the drug because they considered it experimental and not medically necessary. Health systems such as Cleveland Clinic and Mount Sinai said they would not administer Aduhelm. In early April 2022, CMS issued its final coverage decision for Aduhelm, limiting Medicare coverage to prescriptions for people who are enrolled in clinical trials. UnitedHealthcare, which had been waiting for the CMS decision, said it would not cover the therapy either.

The CMS decision is likely to have a big impact, notes Supriya Munshaw, Ph.D., a senior lecturer at the Johns Hopkins Carey Business School. “A lot of private payers were waiting to see what CMS was going to say. This will affect other decisions to cover the drug as well.”

“This was expecting a lot more adoption” Munshaw continues. “A $20,000 drug that is not going to be reimbursed will certainly affect how many patients will be able to use it, because not many patients can afford this out of pocket.”

Biomarker controversy

Munshaw says Aduhelm’s woes can be traced to data from the two pivotal studies showing only a marginal effect on a biomarker, which not everyone agrees is a good indicator of the drug having a positive effect on the cognitive difficulties caused by Alzheimer’s.
“A lot of other private payers were waiting to see what CMS was going to say. This will affect other decisions to cover the drug (Aduhelm) as well.”

—SUPRIYA MUNSHAW, PH.D., JOHNS HOPKINS CAREY BUSINESS SCHOOL

“Aduhelm had excited researchers when early data showed that not only could it block the production of beta amyloid plaques but it also could clear some existing ones. Biogen’s two studies were designed to assess the impact of Aduhelm on cognitive function using the Clinical Dementia Rating Scale Sum of Boxes score, an integrated scale that assesses function and cognition. Other outcomes that assessed behavior and biomarker end points were also used. But both studies were stopped when they were at their halfway point of enrollment. A pooled analysis showed only one study had met its end point.

Biogen has recently begun enrolling patients for a phase 4 confirmatory trial of Aduhelm. Researchers eventually will enroll 1,500 patients with early Alzheimer’s disease in the study, with a primary clinical end point at 18 months after treatment initiation. Biogen expects the study to be completed in about four years. It will use the same end point scale as the previous studies and will also include a trial extension to collect longer-term treatment data for up to 48 months. Biogen also indicated that about 18% of participants enrolled will be Black/African American and Latino.

ICER scrutiny

Aduhelm’s downward arc may make the findings somewhat anticlimactic, but ICER is planning to do a cost-effectiveness evaluation of Aduhelm compared with two as yet unapproved Alzheimer’s therapies, Eli Lilly’s donanemab and Eisai’s lecanemab. Originally, ICER planned to discuss the findings of its report during a meeting scheduled for July 2022, but it has been moved to the first quarter of 2023. Eisai, a Japanese company and a partner of Biogen, completed a rolling submission in May 2022 for an accelerated approval of lecanemab, a monoclonal antibody that targets beta amyloid, to treat patients with early Alzheimer’s disease. Eisai has requested a priority review. The company’s application is based on data from a phase 2b trial in patients with confirmed presence of beta amyloid plaques in the brain, an open-label extension study, and a confirmatory phase 3 trial.

Results from a simulation model conducted by Eisai, published in April 2022 in Neurology and Therapy, found that lecanemab can potentially slow the rate of disease progression, maintaining treated patients for a longer duration in earlier stages of Alzheimer’s disease. In this projection, the mean time to advancing to mild, moderate and severe Alzheimer’s dementia was longer for patients in the lecanemab group than for patients in the standard of care group by two and half years.

Eisai is continuing with a confirmatory phase 3 study of lecanemab with results expected in the fall of this year. The FDA has agreed that this trial could be used to verify clinical benefit.

Eli Lilly announced separately in fall 2021 that it had begun a rolling submission to the FDA for donanemab, which also acts on beta amyloid, for accelerated approval. The company intends to complete its submission in the second quarter of 2022, which could result in an FDA decision in early 2023. Lilly also plans to conduct a phase 3, head-to-head clinical trial comparing donanemab with Aduhelm. This open-label study will enroll 200 patients and will assess plaque clearance of the two therapies based on positron emission tomography scans.

Denise Myshko is senior editor of Formulary Watch®, a news website affiliated with Managed Healthcare Executive®.
For your appropriate members with uncontrolled moderate-to-severe atopic dermatitis (AD)

**APPROVED FOR A BROAD AGE RANGE**

6+ YEARS OF AGE

Real adult and adolescent patients treated with DUPIXENT. Individual results may vary. Child is not an actual patient.

**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 adult and pediatric 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 anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. 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 compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period. Conjunctivitis and keratitis have been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis patients. Some patients reported visual disturbances (e.g. blurred vision) associated with conjunctivitis or keratitis. Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate.

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

**TRIAL RESULTS:** The primary endpoint in CHRONOS and AD-1526 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 CHRONOS. P=0.0001; and 24% of adolescents treated with DUPIXENT vs 2% with placebo in AD-1526, P=0.001). In AD-1652, the primary endpoint was change from baseline in the proportion of subjects with an IGA 0 or 1 at Week 16 (59% 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 CHRONOS. P=0.0001; 42% of adolescents treated with DUPIXENT vs 8% with placebo in AD-1526, 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 AD-1652); and itch reduction defined by ≥4-point improvement in the Peak Pruritus NRS at Week 16 (59% of adults treated with DUPIXENT + TCS vs 20% with placebo + TCS in CHRONOS, P=0.0001; 37% of adolescents treated with DUPIXENT vs 5% with placebo in AD-1526, P=0.001: 61% 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 AD-1652). CHRONOS also assessed endpoints at Week 52. IGA: 36% of adults treated with DUPIXENT + TCS vs 15% with placebo + TCS. EASI: 75% of adults treated with DUPIXENT + TCS vs 22% with placebo + TCS. Peak Pruritus NRS: 51% of adults treated with DUPIXENT + TCS vs 13% with placebo + TCS. P=0.0001. In CHRONOS, 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 + TCS vs 8% with placebo + TCS (P=0.0013).

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

**WARNINGS AND PRECAUTIONS (cont’d)**

**Risk Associated with Abrupt Reduction of Corticosteroid Dosage:** Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation of DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a healthcare provider. 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 Co-morbid Asthma:** Advise patients not to adjust or stop their asthma treatments without consultation with their physicians.

**Arthralgia:** Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization. Advise patients to report new onset or worsening joint symptoms. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.

**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.

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SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Please see additional Important Safety Information below.

TRIAL DESIGNS: A total of 251 adolescents in AD-1526, 367 children (6-11 years of age) in AD-1652 (16 weeks each), and 421 adults in CHRONOS (52 weeks) with moderate-to-severe atopic dermatitis inadequately controlled with topical prescription therapies were randomized to DUPIXENT or placebo. All patients in CHRONOS and AD-1652 received concomitant TCS. All DUPIXENT-treated adults and adolescents ≥60 kg received 300 mg Q2W after a 600 mg loading dose; Adolescents <60 kg and children ≥30 kg but <60 kg received 200 mg Q2W after a 400 mg loading dose. Children 15 kg but <30 kg received 300 mg Q4W after a 600 mg loading dose. In CHRONOS and AD-1526, patients had moderate-to-severe disease with an IGA score ≥3 (overall lesion severity scale of 0 to 4), an EASI score ≥16 on a scale of 0 to 72, and EASI involvement ≥10%. In AD-1652, patients had an IGA score of 4 (severe), an EASI score ≥23, and EASI involvement ≥50% at baseline. 50% of adults and 45% of adolescents had an IGA score of 3 (moderate). 50% of adults and 45% of adolescents had an IGA of A4 (severe). Mean EASI score was 31 for adults, 36 for adolescents, and 37.9 for children; weekly averaged Peak Pruritus NRS was 7.7 for adults, 8 for adolescents, and 7.8 for children, on a scale of 0 to 10.

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.

USE IN SPECIFIC POPULATIONS

- Pregnancy: A pregnancy exposure registry monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. To enroll or obtain information call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/. 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 adult and pediatric 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.

**4 CONTRAINDICATIONS**

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

**5 WARNINGS AND PRECAUTIONS**

**5.1 Hypersensitivity**

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see Adverse Reactions (6.1, 6.2, 6.3)].

**5.2 Conjunctivitis and Keratitis**

 Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT compared to those who received placebo. 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)].

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis patients. Some patients reported visual disturbances (e.g., blurred vision) associated with conjunctivitis or keratitis. Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate [see Adverse Reactions (6.1)].

**5.5 Risk Associated with Abrupt Reduction of Corticosteroid Dosage**

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

**5.6 Patients with Co-morbid Asthma**

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

**5.7 Arthralgia**

Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms, some cases resulted in hospitalization [see Adverse Reactions (6.1)]. In postmarketing reports, onset of arthralgia was variable, ranging from days to months after the first dose of DUPIXENT. Some patients’ symptoms resolved with continued treatment with DUPIXENT and other patients recovered or were recovering following discontinuation of DUPIXENT. Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.

**5.8 Parasitic (Helminth) Infections**

Patients with known helminth infections were excluded from participation in clinical studies. 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 anthelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

**5.9 Vaccinations**

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT. Avoid use of live vaccines in patients treated with DUPIXENT. It is unknown if administration of live vaccines during DUPIXENT treatment will impact the safety or effectiveness of these vaccines. Limited data are available regarding coadministration of DUPIXENT with non-live vaccines [see Clinical Pharmacology (12.2) in the full prescribing information].

**6 ADVERSE REACTIONS**

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

- Hypersensitivity [see Warnings and Precautions (5.1)]
- Conjunctivitis and Keratitis [see Warnings and Precautions (5.2)]
- Arthralgia [see Warnings and Precautions (5.7)]

**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 long-term safety of DUXIPENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1652). The safety profile of DUXIPENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1526. The long-term safety profile of DUXIPENT observed in pediatric subjects 12 to 17 years of age was consistent with that seen in adults with atopic dermatitis.

Specific Adverse Reactions

Conjunctivitis and Keratitis

In adult subjects with atopic dermatitis, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (6 per 100 subject-years) during the 16-week treatment period of the monoclin therapy trials (SOLO 1, SOLO 2, and AD-1021). During the 52-week period of concomitant therapy atopic dermatitis trial (CHRONOS), conjunctivitis was reported in 16% of the DUXIPENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (9 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (AD-1225), conjunctivitis was reported in 20% of the DUXIPENT group (12 per 100 subject-years). In DUXIPENT atopic dermatitis maintenance therapy trial (SOLO 1, SOLO 2, and AD-1021) through Week 16, keratitis was reported in <1% of the DUXIPENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis DUXIPENT + TCS trial (CHRONOS), keratitis was reported in 4% of the DUXIPENT + TCS group (4 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-years). Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUXIPENT compared to conjunctivitis was the most frequently reported eye disorder. During the long-term OLE trial with data through 148 weeks (AD-1225), keratitis was reported in 3% of the DUXIPENT group (2 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see Warnings and Precautions (5.2)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUXIPENT groups in the atopic dermatitis trials. The rates remained stable through 148 weeks in the long-term OLE trial (AD-1225).

Herpes zoster was reported in <1% of the DUXIPENT groups (1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week treatment period of the monoclin therapy trials. In the 52-week DUXIPENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUXIPENT + TCS group (1 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (AD-1225), 1.9% of DUXIPENT-treated subjects reported herpes zoster (0.99 per 100 subject-years of follow up).

Hyper敏sensitivity Reactions

Hyper敏sensitivity reactions were reported in <1% of DUXIPENT-treated subjects. These included anaphylaxis, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum, and erythema multiforme [see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)].

Eosinophils

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 (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. Across all indications, the incidence of treatment-emergent eosinophilia (>500 cells/mcL) was similar in DUXIPENT and placebo groups. Treatment-emergent eosinophilia (≥500 cells/mcL) was reported in <3% of DUXIPENT-treated subjects and <0.5% in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DR12544, QUEST, and VOYAGE). Sinositis (SINUS-2). Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

Carcinoma of the CV

In the 1-year placebo controlled trial in subjects with atopic dermatitis (CHRONOS), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUXIPENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUXIPENT + TCS 300 mg OW 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) production in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies 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 to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 to 11 years of age with atopic dermatitis who received DUXIPENT 200 mg Q2W or 300 mg Q4W for 16 weeks. Approximately 16% of pediatric subjects 12 to 17 years of age with atopic dermatitis who received DUXIPENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; ~3% exhibited persistent ADA responses, and ~5% had neutralizing antibodies.

Regardless of age or population, ~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 titers detected in both DUXIPENT and placebo subjects were mostly low. In subjects who received DUXIPENT, development of high 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 estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: angioedema [see Warnings and Precautions (5.1)]

Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

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/ongoing-study/dupixent/ 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 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, DUXIPENT may be transmitted from the mother to the developing fetus. In an enhanced 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 background risk for 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.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses 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 embryofetal development or body weight or body weight gain were observed. All pregnancies had 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.

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 development 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 effectiveness 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 AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis and AD-1652 which included 367 pediatric subjects.
subjects 6 to 11 years of age with severe atopic dermatitis. The safety and effectiveness 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 AD-1434, an open-label extension study that enrolled subjects who completed AD-1526 and AD-1652. AD-1434 included 136 pediatric subjects 12 to 17 years of age from AD-1526 and 110 pediatric subjects 6 to 11 years of age from AD-1652 with moderate atopic dermatitis at enrollment into the extension study. AD-1434 included 64 pediatric subjects 12 to 17 years of age from AD-1526 and 72 pediatric subjects 6 to 11 years of age from AD-1652 with severe atopic dermatitis at enrollment. No new safety signals were identified in AD-1434 [see Adverse Reactions (6.1)].

Safety and effectiveness in pediatric patients younger than 6 years of age with atopic dermatitis have not been established.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Clinical studies of DUPIXENT in atopic dermatitis did not include sufficient numbers of subjects aged 65 years and over 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 DUPIXENT overdose. In the event of overdose, contact Poison Control (1-800-222-1222) for the latest recommendations and 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 DUPIXENT during pregnancy. Encourage participation to inform their healthcare provider that they are taking DUPIXENT prior to a potential pregnancy.


Administration Instructions

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

Hypersensitivity

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

Conjunctivitis and Keratitis

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

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic, or inhaled corticosteroids except under the direct supervision of a healthcare provider. 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 Co-morbid Asthma

Advise patients with atopic dermatitis who have co-morbid asthma to adjust or stop their asthma treatment without talking to their healthcare providers [see Warnings and Precautions (5.6)].

Arthralgia

Advise patients to report new onset or worsening joint symptoms to their healthcare provider [see Warnings and Precautions (5.7)].

Parasitic (Helminth) Infections

Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection [see Warnings and Precautions (5.7)].

Vaccinations

Advise patients that vaccination with live vaccines is not recommended immediately prior to and while they are receiving DUPIXENT. Instruct patients to inform their healthcare provider that they are taking DUPIXENT prior to a potential vaccination [see Warnings and Precautions (5.9)].
Enbrel stays above the biosimilar fray, but Humira biosimilars may nip at its heels

Amgen’s biologic won’t have biosimilar competition till 2029. But the advent of up to 11 Humira biosimilars next year may put some downward pressure on Enbrel’s price. by TONY HAGEN

Although a 2021 U.S. District Court decision quashed hopes that a biosimilar of Enbrel (etanercept), a rheumatoid arthritis drug, would reach the U.S. market before 2029, biosimilar competition for Humira (adalimumab) may bring down Enbrel’s price in the meantime, experts told Managed Healthcare Executive®.

The prices for Humira and Enbrel have “shadowed” each other very closely over almost 20 years, and next year Humira will face biosimilar competition for the first time. As many as 11 biosimilars to Humira could come on the market in 2023. If they pull down the price of Humira as biosimilars are intended to, then Amgen, which makes and markets Enbrel, could be forced to lower the price of its drug to compete. The current list price for an annual supply of Enbrel is about $83,000.

Health economist Alice M. Ellyson, Ph.D., an acting assistant professor of pediatrics at Seattle Children’s Hospital, has studied the pricing of Humira and Enbrel. “It’s hard to be certain,” says Ellyson about an Enbrel price drop, “but the structure of insurance and the way in which companies negotiate drug prices does kind of incentivize this.” Amgen CEO Robert A. Bradway testified that to offer the same size rebates that competitors such as AbbVie are offering for Humira, his company has to charge the same list prices. For example, in 2018, AbbVie increased the price of Humira by 9.7%, and Amgen followed shortly afterward with a price hike of exactly 9.7% for Enbrel, according to a 2020 investigation conducted by congressional Democrats.

U.S. physicians need to be “in the driver’s seat” and switch their patients from Enbrel to lower-cost alternatives, such as Humira biosimilars, say rheumatologists Mike Schweitz, M.D., secretary and treasurer of the Alliance for Transparent and Affordable Prescriptions (ATAP), and Brett Smith, D.O., a member of the ATAP executive committee and president of the Tennessee Rheumatology Society. Schweitz and Smith say, though, PBMs may dictate that higher list-price medicines be used with their formulary decisions.

Moreover, they note that Enbrel and Humira are not perfectly interchangeable. “It takes more than one drug to find the one that works,” says Schweitz. “When you find that one, the last thing you want to do is switch.”

Still, as more physicians become comfortable with prescribing biosimilars for rheumatoid arthritis, the competition will inevitably put downward pressure on the price of Enbrel, Smith says. “There is some irony in the current situation, he notes.

A 2021 study she co-authored with Anirban Basu, Ph.D., M.S., a professor of health economics at the University of Washington School of Pharmacy, highlighted a tendency for originator companies to raise prices in anticipation of the arrival of biosimilars. “Most of these companies are publicly traded and their stock value declines when their revenues decline, so there’s certainly incentive to get in that short-term revenue by increasing price, even if in the long term it’ll lower their profits,” observes Ellyson.

Tony Hagen is a medical, business and environmental editor and writer in Florence, New Jersey.
States looked to Medicaid managed care plans to control costs and provide some predictability. Now a growing number are asking questions of the plans, and new federal reporting requirements are being implemented.

by JOSEPH BURNS
In late April, California’s Department of Health Care Services said it was investigating Centene Corporation, the nation’s largest managed Medicaid contractor. Under the state’s contract with Centene, California paid the company $6.8 billion last year to manage its Medicaid program and provide care for its 2.14 million California beneficiaries. A Centene spokesperson said, “We have not reached a settlement with the state of California on this issue, and we respect the deep and critically important relationships we have with our state partners.”

To date, Centene has disclosed that it set aside $246.4 million to settle allegations of fraud in four states: Arkansas, Mississippi, Ohio and Kansas. In addition, three states—Georgia, South Carolina and Indiana—also are investigating the insurer over its now-defunct Envelope Pharmacy Solutions, a PBM, according to reports. In response, the Centene spokesperson said, “The no-fault agreements we have with other states reflect the significance we place on addressing their concerns and our ongoing commitment to making the delivery of healthcare local, simple and transparent. Importantly, this allows us to continue our relentless focus on delivering high-quality outcomes to our members.”

One of the earliest investigations of Medicaid managed care insurers’ relationships with PBMs came in 2018 when reporting in The Columbus Dispatch newspaper prompted the Ohio legislature to investigate CVS Caremark, the PBM division of CVS Health. That investigation resulted in Ohio’s Medicaid program ordering five health insurers to end contracts they had with PBMs.

**State-by-state trend**

It would have been impractical for Ohio to end its contracts with health plans. Simply put, state officials needed those companies to manage the care of more than 3 million state Medicaid beneficiaries, among the costliest members of any health system.

Since the late 1980s, 40 states and the District of Columbia have contracted with comprehensive managed care programs. They have done so for a variety of reasons, says Allan Baumgarten, a health policy analyst, consultant and expert in Medicaid contracting. One reason: “States want to be able to predict how much they will spend on their Medicaid programs,” he explains. State Medicaid directors also wanted managed care companies to establish networks, negotiate with providers, oversee referrals to specialists, and control utilization, Baumgarten adds. Seeing these advantages, Medicaid officials in Minnesota and other states began contracting with managed care organizations, he says. State officials also wanted to

“State officials reasoned that managed care was containing costs for employers (and) we should embrace managed care as a solution for the state as an employer.”

—ALLAN BAUMGARTEN, HEALTH POLICY ANALYST AND CONSULTANT
limit the use of emergency rooms by enrolling beneficiaries in primary care homes. Managed care plans already had networks in most markets and statewide contracts to serve employers, explains Baumgarten. “It happened on a state-by-state basis.” After Minnesota, Wisconsin was an early adoptor of Medicaid managed care, in part because there was a strong emphasis among the state’s employers to contract with these plans for their workers, he says. Also, Wisconsin had large hospital systems that started their own health plans, particularly in Madison, the Green Bay area and in Marshfield where the Marshfield Clinic Health System was started. “State officials reasoned that managed care was containing costs for employers (and) we should embrace managed care as a solution for the state as an employer,” Baumgarten says. “After moving large numbers of state employees into managed care plans, the state did the same for its Medicaid population.”

According to the Kaiser Family Foundation (KFF), 40 states and the District of Columbia have what the foundation experts call comprehensive risk-based managed care programs through plans that use capitated per member per month payment for each adult and child under care. Under capitation, managed care plans assume the financial risk for providing healthcare services to all members.

Some of the states also use primary care case management (PCCM) and other programs that are not capitated to manage healthcare costs for Medicaid members, says Andy Schneider, a researcher at the Georgetown University McCourt School of Public Policy and a former senior advisor at CMS, where he focused on Medicaid program integrity. In addition to providing comprehensive acute care, some Medicaid plans also provide long-term services in exchange for a capitated payment for each member.

Among the 10 states that do not have comprehensive managed care programs, KFF reported that four have no Medicaid managed care contracts (Alaska, Connecticut, Vermont and Wyoming) and six have PCCM and other similar programs (Alabama, Idaho, Maine, Montana, Oklahoma and South Dakota).

Some states carve out services such as behavioral health, pharmacy benefits, dental care and long-term care from their managed care contracts and pay fee for service for those services, KFF noted. However, more states were beginning to include these services in managed care organization (MCO) contracts, including 35 states that had pharmacy benefits in managed care agreements as of July 2021. There is some movement toward splitting off pharmacy benefit management. Three states (California, New York and Ohio) will carve out pharmacy benefits from their MCO contracts.
Medicaid directors prepare for the end of the Public Health Emergency

Unless the coronavirus wreaks more havoc on the nation’s healthcare system, the public health emergency (PHE) may end in the coming weeks or months. When it does, some 14 million Medicaid members who enrolled after the PHE began in February 2020 may lose their health insurance.

The Families First Coronavirus Response Act of 2020 required states to implement a continuous coverage requirement to ensure that workers who lost their jobs or employer-provided coverage would have insurance through Medicaid or some other source. The law also provided a temporary increase of 6.2% in federal Medicaid payments so that states could maintain continuous Medicaid enrollment for nearly all enrollees.

This requirement has been largely responsible for a 20% increase in enrollment in Medicaid and the Children’s Health Insurance Program (CHIP) since February 2020. The most recent estimate from the Kaiser Family Foundation put the number of Medicaid and CHIP members at 85.8 million as of November 2021, an increase of 14.1 million from early in 2020.

State Medicaid directors are taking steps now to do what they can to keep as many of those members enrolled in some form of health insurance.

Before the pandemic, states reviewed the income, age or disability status of those enrolled to see if they continued to qualify for the state and federal safety net program. That review was suspended during the PHE. But now state Medicaid officials face the significant task of reevaluating each person’s eligibility. Some state officials may also be assisting those enrollees in finding new jobs or new forms of health insurance or both, according to Kaiser Health News.

That means that those who gained coverage during the PHE cannot earn so much that they would no longer qualify for Medicaid. It also means they must provide whatever information states require to verify income or residency, Kaiser Health News reported.

Those most at risk are Medicaid members who are also eligible for Medicare, often referred to as dual eligible. The health policy journal Health Affairs noted that such individuals could be disproportionately harmed by unnecessary disruptions in Medicaid coverage.

Many Medicaid beneficiaries who gained coverage during the PHE may be able to enroll in plans through the ACA marketplaces, says Katherine Hempstead, a senior policy adviser for the Robert Wood Johnson Foundation.

“They may be able to get affordable insurance coverage through the marketplace because Congress increased the tax credits under the American Rescue Plan Act of 2021,” she adds. Also, some low-income Medicaid members may qualify for coverage that does not require a premium payment, she says.

Still, Hempstead is concerned for those Medicaid members who may not be able to afford coverage if the increased credits expire at year-end unless Congress extends them. If the tax credits are not renewed, many Medicaid members may be reluctant to buy health insurance on the marketplace because they would need to make premium payments, she notes.
“The problem is once you open the door to the intermediation of health plans, you create opportunities for gaming the system.”

—DONALD BERWICK, M.D., M.P.P., FORMER CMS ADMINISTRATOR

15%, followed by Anthem, with 11%. These were followed by UnitedHealth Group, with 9%; Wellcare, with 7%; Molina, with 5%; and CVS Health (which owns Aetna), with 3%, KFF reported. In January 2020, Centene acquired Wellcare.

Given Schneider’s background in Medicaid program integrity, it seemed obvious to ask if those health insurers and PBMs have found ways to boost profits by using their MLR calculations to their advantage.

“That’s a good question,” Schneider says. He would not comment, however, on whether managed care plans have abused the MLR program but did note that insurers and their subsidiaries have ways of doing so. By acquiring PBMs, physician groups, and other healthcare provider organizations, such as home health companies, health insurers can report payments to those organizations as healthcare spending for beneficiaries.

In the Louisiana lawsuit against UnitedHealthcare and OptumRx, the state charged that payments to OptumRx were used to boost expenses when, the lawsuit alleges, those payments to United’s subsidiary PBM helped to increase the profit for both the PBM and the parent company.

Making such payments to a subsidiary could benefit Medicaid managed care plans because under the MLR rules in many states, these plans cannot spend more than 15% of revenue on administrative costs and profits, Schneider says. “By paying themselves for delivering services to enrollees, MCOs can make money on their provider operations and, at the same time, help themselves hit the 85% MLR target,” he explains. A managed care plan that does not spend 85% on care and other related expenses would need to rebate any excess to the state.

The MLR rules are different for plans sold in the individual market under the Affordable Care Act because any spending below the required percentage would go back to health plan members, he adds.

Calculating medical losses
Each MCO is required to file an annual MLR report that must show the MLR calculations and specific data behind those numbers, Schneider says. In the calculations, the amounts paid for medical care are considered losses and any remaining premium revenue can be spent on administrative costs or retained as profit, or for nonprofit insurers, retained as a surplus, he adds.

Investors prefer that publicly traded companies have low MLRs. Thus, if administrative costs are kept in check, more premium revenue can be paid to shareholders, he explains.

For Medicaid managed care plans, the MLR numerator must show funds paid for covered services, for improving quality and for fraud prevention. The denominator is the amount received in capitation payments minus any funds paid in taxes or for licensing, regulatory fees or assessments.

“They can’t manipulate what they get in capitation revenue or what they pay in taxes and fees, and they usually don’t spend much on fraud prevention,” Schneider says. “Quality improvement and payments to providers are really where they put their money.”

Once they tally all payments to providers and for quality improvement and fraud prevention, managed care plans have no other options to increase expenses. “If you’re a large, publicly traded health company with lots of resources, you can buy your own providers, meaning physician groups or pharmacy benefit managers,” he suggests. “Then you can pay them more.”

Baumgarten agrees, saying, “Profits and administrative expenses can be a way of moving money to owned or affiliated companies.”

What’s unknown is whether UnitedHealthcare of Louisiana paid OptumRx more than it would have paid a PBM that was not a subsidiary, Schneider says. “I don’t know what happened in the Louisiana case, but you can certainly see how the incentives are aligned,” he adds.

An independent audit from an accounting firm in Atlanta showed that in 2019, UnitedHealthcare of Louisiana had an MLR of 93%. This percentage exceeds the CMS minimum requirement of 85%, the auditors reported.

Increased reporting
One way that states can ensure that managed care plans are delivering high-quality, coordinated and comprehensive care to Medicaid beneficiaries is to require these plans to
Increased scrutiny is coming from state and federal regulators later this year when CMS implements new data-reporting tools for managed care programs that contract with state Medicaid programs, Libersky says.

In a memo in June 2021, the federal Center for Medicaid and CHIP Services (a division of CMS) issued a bulletin explaining the requirements Medicaid managed care plans must follow to comply with the 2016 Medicaid and CHIP Managed Care final rule. CMS published that rule on April 25, 2016, to align the regulations that govern the Medicaid and CHIP programs with those that control other U.S. health insurance programs.

The rule also was designed to improve how states purchase managed care for beneficiaries and to introduce new consumer protections for members, Libersky says. Most of the data CMS wants from states are not new because managed care plans and the states have already been collecting that information. But now they will be required to report that data to CMS, allowing the states to improve compliance with managed care standards and requirements, she adds.

“It’s a big deal,” Libersky says of the new tools the states and federal regulators will use to monitor and oversee managed care programs for Medicaid and CHIP.

Starting at the end of this year, health insurers that have contracts with states ending on June 30, 2022, will need to file the first of what CMS calls the “Managed Care Program Annual Report.” Plans with contracts that end on Aug. 31, 2022, will need to file their oversight and management reports by the end of February 2023. All plans will need to file their reports by the end of September 2023, CMS said.

The data in these reports will allow state and federal regulators to know much more about how each MCO operates on a variety of performance measures. These include enrollment, MLRs, quality improvement efforts and network adequacy, among other data, Libersky notes.

Given the problems that state Medicaid programs have uncovered about how managed care plans and their subsidiaries operate, increased reporting requirements for managed care insurers is a positive development, Schneider says. “Under the 2016 rules, states aren’t required to set a minimum MLR, but if they do, it can’t be lower than 85%,” he explains. “Also, even if they set a minimum MLR, they don’t have to collect a remittance if the MCO doesn’t hit that percentage.” Regardless of whether a state sets or enforces a minimum MLR, all states must assume an 85% MLR when setting capitation rates, and each MCO must file an annual MLR report according to federal regulations, he adds.

Libersky explains further, saying, “The expectation is that the states will be better able to see how insurers are spending their premium income but also that states may be able to recoup some money if the managed care plans are not meeting those ratios.”

CMS will also be collecting information on network adequacy and access to care, she says.

Need for coordinated care

Former CMS Administrator Donald Berwick, M.D., M.P.P., agrees that any focus on improving care is good for Medicaid beneficiaries. After all, Medicaid members need some of the most intense and costly healthcare services that the delivery system can provide, notes Berwick, a lecturer in the Department of Health Care Policy at Harvard Medical School.

“They’re a highly vulnerable population that often have complex healthcare needs and require many different medical and social services,” he says. “Therefore, it makes a lot of sense to offer Medicaid beneficiaries the advantages of truly coordinated care that managed care organizations provide.”

Outside of MCOs, the healthcare systems are complex and fragmented, which may not serve the nation’s Medicaid members well, he adds. “There’s some logic to contracting with managed care companies,” he notes, citing Kaiser Permanente, Group Health Cooperative of Puget Sound and HealthPartners in Minneapolis as examples of well-run MCOs.

“The problem is once you open the door to the intermediation of health plans, you create opportunities for gaming the system,” he says. “That said, you can’t throw up your hands and say we shouldn’t be helping to manage the care of these patients. That would be wrong because Medicaid members need the help that coordinated care systems provide.”

Joseph Burns is an independent journalist in Brewster, Massachusetts, who covers healthcare, health reform and health insurance.
The 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

For the treatment of patients with metastatic BCC (mBCC) previously treated with an HHI or for whom an HHI is not appropriate. The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit

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

Visit LIBTAYOhcp.com for more information.

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.
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% (25/810) 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 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. Hyperthyroidism 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 0.6% (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%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated 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%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 11% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

  - **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% (1/810) 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 fatal (0.1%), Grade 3 (0.1%), and Grade 2 (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**: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre 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 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, 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 (mSCC) or locally advanced SCC (lSCC) 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 (lBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- with metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for the mBCC indication may be contingent upon verification and description of clinical benefit.

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

None.

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-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 reinitiated 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 reinitiated 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 reinitiated 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. Withhold 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 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 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].

5.2 Infusion-Related Reactions

Endocrine:

Other immunosuppressants and the absence of a clear alternate etiology. 

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 reinitiated 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. Withhold 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 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 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].
Hypophysisis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysisis led to permanent discontinuation of LIBTAYO in 0.1% patient and withholding of LIBTAYO in 0.1% patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysisis. Hypophysysis has 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 [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 has 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%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in 3.8% (1/26) of patients with hypothyroidism. Hypothyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reintiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

**Hyperthyroidism:** Hyperthyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hyperthyroidism led to permanent disconituation of LIBTAYO in 1 (0.1%) patient. Hyperthyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hyperthyroidism. Hyperthyroidism resolved in 83.3% of the 60 patients. The majority of patients with hyperthyroidism 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. Eosinophilic 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. Uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada. Hogue. 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/polyomyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immunne): Hemolytic anemia, aplastic anemia, hemorrhagic/lymphohistiocytosis, 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. Interupt 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 Allogenic 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 allogenic 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 allogenic 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 reactions 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), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥6 months and 22% were exposed for ≥12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypotremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cutaneous Squamous Cell Carcinoma (CSCC)
The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Studies (14.1) in the full prescribing information]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had lCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks 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, sepsis, 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, ardalgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, proctitis, and confusion.

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, pneumonia, sepsis, skin infection, and hypercalcemia. The most common (≥4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hypotremia, 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 Reaction</th>
<th>LIBTAYO N=219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General and Administration Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashp</td>
<td>31</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pruritusa</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrheap</td>
<td>25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nauseap</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased INR</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal paina</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>0</td>
<td></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 cough and productive cough.
- b. Composite term includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematosus, rash macular, rash pruritic, drug eruption, pruritis, and skin reaction.
- c. Composite term includes pruritus and pruritus allergic.
- d. Composite term includes diarrhea and colitis.
- e. Composite term includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain.
- f. Composite term includes cough and upper airway cough syndrome.

### Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased INR</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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

### Basal Cell Carcinoma (BCC)
The safety of LIBTAYO was evaluated in 132 patients with advanced BCC (mBCC N=48, lBCC N=84) in an open-label, single-arm trial (Study 1620) [see Clinical Studies (14.2) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks as an intravenous infusion for up to 93 weeks or until disease progression or unacceptable toxicity. The median duration of exposure was 42 weeks (range: 2.1 weeks to 94 weeks).

The safety population characteristics were: median age of 68 years (38 to 90 years), 67% male, 74% White, and ECOG performance score (PS) of 0 (62%) and 1 (38%).

Serious adverse reactions occurred in 32% of patients. Serious adverse reactions that occurred in ≥1% of patients were urinary tract infection, colitis, acute kidney injury, adrenal insufficiency, anemia, infected neoplasm, and somnolence. Fatal adverse reactions occurred in 1.5% of patients who received LIBTAYO, including acute kidney injury and cachexia.

Permanent discontinuation of LIBTAYO due to an adverse reaction occurred in 13% of patients. Adverse reactions resulting in permanent discontinuation of LIBTAYO in ≥1% (at least 2 patients) were colitis and general physical health deterioration.

Dosage delays of LIBTAYO due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage delay in ≥2% of patients (at least 3 patients) included blood creatinine increased, diarrhea, colitis, fatigue, headache, pneumonia, and urinary tract infection.
The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection.

The most common Grade 3 or 4 adverse reactions (> 2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypokalemia and visual impairment. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia.

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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>49</td>
<td>3.8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal painb</td>
<td>33</td>
<td>1.5</td>
</tr>
<tr>
<td>Upper respiratory tract infectionsc</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashd</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysepnex</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensione</td>
<td>11</td>
<td>4.5</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 acniform, 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

g. Cough is a composite term that includes cough and productive cough

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 graded per NCI CTCAE v.4.03

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 pneumonia, 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 Grades 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>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grades 3-4 %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscleoskeletal pain</td>
<td>26</td>
<td>0.6</td>
<td>27</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>1.4</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
<td>26</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
<td>50</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysepnex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

g. Cough is a composite term that includes cough and productive cough

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

a. Muscleoskeletal pain is a composite term that includes back pain, arthritis, chest pain, neck pain, myalgia, radicular, skin pain, and spinal pain

b. Rash is a composite term that includes rash maculo-papular, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, drug eruption, dermatitis herpetiformis, and skin eruption

c. Fatigue is a composite term that includes fatigue, asthenia, and malaise

d. Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, and respiratory tract infection

e. Cough is a composite term that includes cough and productive cough
therefore, LIBTAYO has the potential to be transmitted from the mother in pregnant women. Animal studies have demonstrated that the full prescribing information. Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

8.2 Lactation
Risk Summary
There is no information regarding the presence of cepimilimab-rcwlc 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

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see Use in Specific Populations (8.1)].

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 patients and younger patients. Of the 219 patients with mCSCC or IaCSCC 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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

Data
Animal Data
Animal reproduction studies have not been conducted with 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 cepimilimab-rcwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Toxicity graded per NCI CTCAE v. 4.03
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

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, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cepimilimab-rcwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cepimilimab-rcwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cepimilimab-rcwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cepimilimab-rcwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
A conversation with Alan Lotvin, M.D., president of CVS Caremark

Alan Lotvin, M.D., has been president of CVS Caremark, the pharmacy benefits management (PBM) division of CVS Health, since 2020 and led the company’s specialty pharmacy business for six years before taking the reins of the PBM. Managing Editor Peter Wehrwein spoke with Lotvin about the industry’s reputation, rebates, industry consolidation and transparency. This a truncated transcript of the interview that has been edited for clarity. A longer version is available on our website under the PBM leaders tab.

I think that PBMs have a really bad reputation as middlemen. I’m curious whether you accept that premise. And if not, why not? Because it would seem to go against a lot of what I’ve read. And if you do accept the premise, are you concerned about it? And what should CVS Caremark and the industry do about it?

Those are all good questions. I would first of say that everyone loves to characterize middlemen, in general — no matter what the industry is — as awful. But are we all going to really get in our car and drive out to the farm and buy food directly from the producer? The barter economy tends not to work. So, yes, we are middlemen.

What I would say is, from a reputation perspective, I do think that the industry has a challenged reputation. I think part of it is that we have very well funded — we’ll just call them rivals, who are trying to distract from the core issue.

(The way I would) characterize it is drug prices are high. Drug spending, which is the total amount of drugs spend, actually isn’t that high.

And if you look back over the last several years, drug spend, year over year, has gone up less than inflation.

That’s largely for a couple of reasons. One, it’s been the influence of generics and, two, is the influence of discounts driven by the PBMs.

So you think about the dynamics of the industry. You have the pharmaceutical industry, which sits with intellectual property-granted, monopoly pricing power. I believe in intellectual property. It is a big driver of innovation. But like any tool, it can be misused.

On the other side, to combat the monopoly pricing, what we and our competitors in the PBM industry do is we aggregate lives, we aggregate people’s purchasing power, so that we can say to a manufacturer, look, we like your drug. But we like drug A and like drug B, (and) they’re kind of the same. And, you know, we need a better price. Or if it’s generic, we’re going to use the generic.

I think it creates this natural tension that upsets the manufacturers a lot. They spend a lot of money. It would be disingenuous of me to disagree with you and say that the industry doesn’t have a poor reputation. I do, completely, think it is undeserved.

As you know, the plan member doesn’t benefit from that difference between the list price and the net price, directly. Their coinsurance is based on the list price. You guys get the rebates, but as Joe citizen, I don’t experience that net price. I know what you’re going to say, that I do, in lower premiums, but that’s rather indirect.

That’s fair. So I would say a couple of things. Ninety-eight percent of the rebates that we generate go back to our clients. Sometimes those go back to members at the point of sale.

Sometimes it goes, to your point, into reducing premiums. That’s absolutely true.

The rebates that we collect — collect on behalf of our customers — lower the overall cost of drugs, lower the net price of drugs.

The other place, though, where you do benefit directly as the individual is the ability to drive greater use of generics. Generics are just much, much less expensive than brands.

So your point is how do we take this rebate, the gross-to-net difference and make it more applicable to the individual?

Let me play you a flip of that, though. The whole principle of insurance is we take all of the costs and we distribute them across a lot of people.

Let’s take two people, person A, who is on an expensive medication that has a copay card from the man-
manufacturer. Person B, who needs to have their hip replaced. Persons A and B, they work for the same employer, they have the same benefit plan.

When Person A goes and has a $1,000 deductible, because of their Humira, or whatever drug they’re taking, if they then get the $1,000 back from the manufacturer or if they got the rebate applied to them, they have lowered their out-of-pocket costs.

The person who has their hip replaced — no one is helping them take care of their deductible, there’s no rebate coming back to them.

So how do you balance this? I think what we have started to think about is how do we think about deductibles. What’s the advice we would give people around high-deductible plans and how to think about minimizing the impact of that drug spending has (when someone has) a high-deductible plan.

The industry has consolidated. We talk about the Big Three. It used to be the Big Five. And market concentration is, generally speaking, a bad thing. It leads to anti-competitive practices. What your response? First of all, I would say this is a really competitive industry and it’s supported by a set of really, really smart consultants who are outstanding at driving down costs every year.

If you listen to our public analyst calls, we talk every year about our price erosion. Every year we talk about how our prices go down.

When I started in this industry, you know, a common price point for retail pharmacy was AWP (average wholesale price) minus 12 for brand drugs. We’re now at average wholesale price minus 19 or 20.

So I think pricing, in general, has continued to come down each year in terms of the discounts off the benchmarks. Now, you could say, “But the benchmarks are going up.” Yes, they have been. I don’t set the benchmarks. AWP is driven by wholesale acquisition costs, which are set by the manufacturers.

Every year there are new entrants in the business. Yes, the Big Three, Big Four, Big Five, for the past whatever amount of time have had 75% of the business. Since Express Scripts and Medco came together in 2010 or so there have been no material mergers of size.

What’s happened is the migration to larger companies because scale really matters in this business. Scale gives you negotiating leverage with manufacturers. Scale gives you negotiating power with retail pharmacies. Scale lets you invest. I mean, we invest more just in our digital properties that talk to patients than we do in our digital properties. Scale gives you negotiating leverage with manufacturers. Scale gives you negotiating power with retail pharmacies. Scale lets you invest. I mean, we invest more just in our digital properties that talk to patients than we do in our digital properties.

Let’s talk about the smaller PBMs. EmsanaRx is a name that has cropped up. It has been started by a purchasing group. It is promising to bring total transparency to the business and subsumed in that promise of transparency is that the PBM industry is opaque. The industry is accused of being opaque and practicing dark arts. How do you respond to that?

I’ll speak to CVS. I can’t really talk to what my competitors are doing in a fair fashion.

We have established an approach that says we are going to be transparent with our customers. Most of our large customers get 100% of rebates pass through to them.

And those that choose not to do that, it’s because they’re saying, “Well, look, you have 14 different pricing levers. You can keep part of the rebate. I want you to give me a discount over here.” And they have audit rights. That’s number one.

Number two, many of our clients have fully transparent retail contracts. There’s no spread pricing.

Then the last part becomes when I go to a client and talk to them, how do I show them that whatever we’re putting on the table is in their interest. So, we show them the math.

This is a good example. So, a few years back, the PSCK9s dropped their price, dramatically. Now, their original price had a rebate associated with it, and we make rebate guarantees. When the price went down, the rebate went down.

We went to our clients and said, “You have a choice here. I can keep the high-rebate, high-price product on — let’s just say for argument’s sake, the net prices were the same; they actually weren’t — or we can put the low-price, low-rebate one on the formulary and just adjust your rebate guarantee.”

So that’s the sort of thing that we’re trying to do. I tell my customers very clearly, I’m a for-profit company. We’re going to make a margin. Our margin is 3.5%, 4%. If that’s too much, let’s talk about it. And I want you to know where I make the margin is somewhere where you understand where it’s coming from.
Evaluating Current and Future Opportunities for HIV PrEP

Appropriate use of PrEP has been proven to significantly reduce the risk of getting HIV; however, only about 1 in 5 persons with an indication for PrEP is receiving it. Numerous factors contribute to both access and adherence to PrEP medications. Addressing educational needs, coverage policies, and therapeutic innovations may increase access to and uptake of PrEP to prevent HIV infection.

Throughout this Population Health Perspectives video series, our expert faculty will discuss the following:

**Population Health in PrEP:**
- Economic impact of HIV
- Challenges and unmet needs

**Patient-Centered Care:**
- Quality of care assessments
- Adherence support and patient education programs

**Patient Access:**
- Disparities and inequities in access
- Utilization management strategies and challenges

**Future Opportunities:**
- New and novel dosage forms
- Potential challenges and logistical concerns for PrEP therapies

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Making contraception more available

Demand for birth control obtained through telehealth or without a prescription continues to grow, even as states battle over abortion rights by SUSAN LADIKA

Access to abortion is being curtailed in many states and the U.S. Supreme Court is considering a challenge to Roe v. Wade. At the same time, other states and organizations are making it easier to obtain contraception and medication abortion drugs.

With increased availability of contraception, “there are certainly (fewer) unwanted pregnancies and abortions,” said Krishna Upadhya, M.D., M.P.H., FAAP, vice president of quality care and health equity at Planned Parenthood Federation of America.

Allowing people to obtain hormonal birth control without a prescription is one way some states have improved access to contraception. In February 2022, North Carolina became the most recent state to enact such a law, which allows people to purchase contraceptive pills and patches at drugstores after consulting with a pharmacist but without a prescription from a doctor. According to the Guttmacher Institute, it’s one of 17 states and the District of Columbia that allow pharmacists to provide birth control, a group that includes right-leaning states such as Arkansas (its regulations are still being developed) and Idaho.

However, a majority of states still require a prescription — that can be a barrier to access for some people, notes Upadhya says. They may lack transportation to get to a healthcare provider or have a busy schedule with work and child care issues. Even if birth control is dispensed at a drugstore without the need for a prescription, it may be difficult to travel to a brick-and-mortar store pharmacy, Upadhya says.

Cost is also an issue, notes Carrie N. Baker, Ph.D., J.D., professor of American studies and professor of the study of women and gender at Smith College. Birth control may not be covered by insurance if it is acquired without a prescription. And some women with insurance still face copays or provider charges, she points out. The Affordable Care Act requires coverage for 18 methods of contraception without cost sharing, but health insurers can use formularies, prior authorization requirements and other restrictions that wind up limiting contraceptive choices, according to the Guttmacher Institute.

**COVID-19 demand**
Women can face other challenges as well when it comes to obtaining contraception. Approximately 19 million women live in contraception deserts, where they “lack reasonable access to healthcare,” says Varsha Rao, MBA, CEO of Nurx, a virtual care startup in San Francisco that focuses on women’s health. Most contraception deserts also have few pharmacies, including rural areas or urban ones that underserve, Rao says.

Nurx was founded in 2015 to help address that shortage by offering a women-focused healthcare platform. Along with providing contraception to residents of almost 40 states, it offers services such as tests for sexually transmitted infections, pre-exposure prophylaxis for HIV, and some migraine and dermatological treatments. Chelsea Clinton, daughter of former President Bill Clinton and vice chair of the Clinton Foundation, is a board member. In February, Nurx merged with Thirty Madison, a specialty healthcare company that has brands that offer care for migraines, hair loss and other conditions.

Nurx provides asynchronous care, meaning the patient provides information about their needs and then a provider reviews it and asks questions if needed before writing a prescription. The birth control is delivered to the patient’s door. Most patients pay with their own money, but the company also accepts insurance.

As the COVID-19 pandemic continued on page 48
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Continued from page 46

swept through the country, Nurx saw demand for contraception jump 50%, Rao says, and requests for emergency contraception jumped 300% as the pandemic made it more difficult for patients to see providers. Emergency contraception, which prevents pregnancy, can involve the insertion of a copper intrauterine device, which prevents sperm from fertilizing an egg, or oral medications such as ulipristal and progestin that inhibit ovulation. Nurx sells the oral medications. The pandemic also led to greater acceptance of telehealth for all purposes. Nurx serves approximately 400,000 consumers each month, and approximately 40% of its patients are in the South.

Planned Parenthood has moved toward providing services remotely. The organization has an app through which residents of 40 states and the District of Columbia can request birth control or emergency contraception. Once they pay, the contraception is mailed to them. Planned Parenthood accepts Medicaid from residents of Michigan, Minnesota and Wisconsin. The organization also has a telehealth option that accepts some health insurance plans.

The effect of abortion restrictions

A ruling from the Supreme Court on in Dobbs v. Jackson Women’s Health Organization is expected in summer 2022. At issue is a Mississippi law that bans almost all abortions after 15 weeks of pregnancy. A leaked version of the court’s draft opinion suggests that it will overturn the Roe v. Wade decision that legalized abortion. If that happens, it will trigger restrictive abortion laws in many states. Others have already enacted new restrictions. According to a Guttmacher tally, nine states have enacted 33 abortion restrictions this year. Among the most restrictive is the law in Texas that bans most abortions as soon as any cardiac activity can be detected, which is at approximately six weeks of pregnancy. Rao says requests for emergency contraception from Texas have nearly doubled since the “heartbeat law” went into effect.

Anti-abortion activists are increasingly focusing on medication abortions, which now account for almost 55% of the abortions in the United States. In Europe they account for 90% of abortions, Baker says. In medication abortion, a drug called mifepristone is taken first. It blocks the production of progesterone so the pregnancy can’t continue to grow. Misoprostol is then taken 24 to 48 hours later, causing cramping and bleeding that empties the woman’s uterus.

Results of a small study reported in the Aug. 24, 2021, issue of JAMA Network Open showed that medication abortion drugs delivered by telehealth was safe and effective. Ushma Upadhyay, Ph.D., M.P.H., an associate professor of obstetrics, gynecology and reproductive science at the University of California, San Francisco, and her colleagues reported that 105 of the 110 participants having a medication abortion had a complete abortion without intervention and the other five required medical care.

Nineteen states require providers to distribute the medication in person, Baker says. Women can get around those rules by going to other states for telehealth abortions, having medication sent to friends in other states or using a mail-forwarding service, she says.

Allowing access to abortions via telehealth reduces travel time and costs for women who don’t live near a clinic and would have to travel elsewhere for care, says Kaori Sueyoshi, M.P.A., M.P.P., director of innovation at Planned Parenthood. And women don’t have to take time off work or find child care, as they would with an in-person abortion.

“It fits the needs of people who are most underserved,” Sueyoshi says. Anti-abortion activists and lawmakers say medication abortion drugs obtained via telehealth subvert state laws, and some states prohibit them. Texas has added fines and possible jail time for anyone who prescribes the pills by way of telehealth or through the mail.

**Pharmacists as providers of contraception:**

**WHAT STATES ALLOW**

17 STATES

and the District of Columbia allow pharmacists to provide contraceptive care.

15 STATES

specify the contraceptive methods that pharmacists are allowed to prescribe.

8 STATES

prohibit or limit pharmacist prescribing for patients who are 17 years old or younger.

7 STATES

require a patient to see a primary care provider after a specific period of time to continue receiving contraceptives from a pharmacist.

Source: Guttmacher Institute

**WHAT STATES PROHIBIT PHARMACIST**

22 STATES

do not allow pharmacists to provide contraceptive care. Yet 20 states and the District of Columbia allow pharmacists to provide contraceptive care. 

Sueyoshi, M.P.A., M.P.P., director of innovation at Planned Parenthood. And women don’t have to take time off work or find child care, as they would with an in-person abortion.

Susan Ladika is an independent journalist in Tampa, Florida, who writes about healthcare and business.
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ACO update: The Pathways to Success program

The program implemented by the Trump administration is designed to put more Medicare Shared Savings Program ACOs into two-sided risk. An industry group has discouraged participation in the program. by ROBERT CALANDRA

Since its inception in 2012-2013, the CMS Medicare Shared Savings Program (MSSP) has cranked along like a roller coaster climbing steadily upward. Starting with 220 participating accountable care organizations (ACOs) and 3.2 million beneficiaries, it reached the high point in 2018 with 561 organizations covering 10.5 million people.

That was the same year that CMS unveiled Pathways to Success, its overhaul of MSSP’s ACO program aimed at increasing cost savings for the Medicare program by requiring more MSSP ACOs to assume two-sided risk: upside “shared savings” if they come in under budget for their attributed population but also downside “shared losses” if they go over it. The number of participating ACOs fell to 487.

Since then, the MSSP ACO program has oscillated between shallow valleys and modest peaks of ACO participation, growing by 30 organizations in 2020, losing 40 in 2021, and adding 6 this year. The number of beneficiaries covered has, though, held relatively steady with 11 million at the beginning of this year, or about one-third of the 33 million beneficiaries in traditional Medicare.

A number of factors contribute to those numbers, including the normal ebb and flow of ACOs joining and leaving the program and consolidation of providers. The winding down of another CMS ACO program, called Next Generation, had some ACOs looking for a new home.

Then there is what David Muhlestein, Ph.D., J.D., calls the “really big driver”: the COVID-19 pandemic. “It has made people completely rethink what their priorities are, and anything related to ACOs is just so much less important right now,” says Muhlestein, chief strategy and chief research officer for Leavitt Partners, a healthcare consulting firm in Salt Lake City.

Jennifer Gasperini, director of regulatory and quality affairs for the National Association of ACOs (NAA-COS) agrees that the pandemic and all those other issues are at play. But the way she sees it, Pathways is the main reason.

“We definitely think that Pathways has had an effect on the overall interest in the program,” she says. “Pathways decreased the incentive to participate by doing two things: reducing the shared savings that you can keep if you are successful and pushing (ACOs) to risk more quickly.”

Two-sided risk sooner

Accelerating assumption of two-sided risk is the most important difference between the Pathways program implemented by the Trump administration and the original MSSP. Pathways sorted the prior MSSP’s multitrack options down to two, Basic and Enhanced, although the Basic Track has five stages. ACOs newly entering the Basic Track have a two-year period of upside-only risk and 40% shared savings. After that, they are on a three-year schedule of two-sided risk that dial up the shared-savings percentages but also creates greater exposure to shared losses.
The Enhanced Track puts ACOs right into two-sided risk with shared savings of 75% and shared losses of between 45% to 75%. But, importantly, the Enhanced Track also qualifies the ACO as an Advanced Alternative Payment Model, which makes it eligible for incentive payments under a different CMS program.

ACOs that were participating in MSSP prior to Pathways could enter the Basic Track at its various stages depending on their revenues, how long they had been participating in MSSP and other factors. According to a CMS report earlier this year, as of Jan. 1, 2022, 337 of the 483 (70%) ACOs in the Pathways version of MSSP were participating in the program’s Basic Track, and 190 (56%) of those were still in the two-year period of one-sided risk. The other 146 jumped right into the Enhanced Track.

Muhlestein is a fan of the Pathways effort to push ACOs into assuming two-sided risk sooner: “I think that making people move toward risk makes it real and requires them to think about things in a way they probably didn’t before,” he says. “I think, basically, it says quit experimenting and start doing, which is a major difference (from) what has happened in the past.”

The Pathways rules also changed some of the benchmarking methods used to set the financial goals of the ACOs and therefore their eligibility for shared savings and losses.

Although NAACOS generally approves of CMS’s benchmarking changes, the group is concerned about what Gasperini dubs the “rural glitch.” For instance, an ACO representing half the care in a smaller region may improve by 5% in a year. That means that, on average, the whole region improved by 2.5%. By exclusively comparing the ACO to its region, the ACO is literally competing against itself.

“This is about the idea of having to constantly kind of beat yourself,” Gasperini says. “That is one issue that we think, if changed, could really go a long way toward sustainability in the program.”

Pathways rules have some benefits for the participating ACOs. They can also permit the bypass some Medicare restrictions on telehealth services. (Because of the COVID-19 Public Health Emergency and its telehealth waivers, the telehealth perk hasn’t meant as much as it might have). Additionally, Pathways waives a Medicare rule that limits coverage of rehabilitation in a skilled nursing facility to beneficiaries who were discharged to the facility after three consecutive days in a hospital. The Pathway rules also allow ACOs to make $20 incentive payments to beneficiaries to take steps such as joining a wellness program that are believed to lower costs and reduce the risk of serious illness.

NAACOS has viewed the declining number of ACOs in MSSP with alarm. When the CMS released the figures earlier this year, NAACOS issued a press release that quoted its chief executive officer, Clif Gaus, Sc.D., M.H.A., as saying they showed a “shrinking of this important ACO model.” According to NAACOS, 18 of 46 new ACOs participating in the program are former Next Generation participants and so not really new ACOs.

Many of NAACOS’s concerns would be remedied if a bipartisan bill stalled in the House were to gain traction. Introduced in July 2021, the Value in Health Care Act of 2021 would bump MSSP’s Basic Track shared-savings rate back to 50% and give ACOs at least three years in the one-sided risk mode.

Meanwhile, NAACOS continues to meet with the Biden administration to discuss adjustments to MSSP ACO, including new incentives and grants that would help attract practices. The administration, Gasperini says, is “engaged with us and, I think, committed to value-based care, and hopes it or CMS, or Congress, will make some changes to Pathways before the end of the year. Now it’s really about putting pen to paper and making some of these changes so that we can see increased participation.”

Like Gasperini and NAACOS, others are also waiting to see which direction the Biden Administration takes with the ACO program.

“The big one is what is the Biden administration plan?” says Muhlestein. “That is really going to influence the next couple of years how much activity takes place and how active people are. I would fully expect them to come up with a full plan, both from the (CMS) Innovation Center as well as CMS for the MSSP.”

Robert Calandra is an independent journalist in the Philadelphia area.
Uterine fibroids (UF), also referred to as leiomyomas or myomas, are benign lesions of the uterus, comprising fibroblasts, smooth muscle cells and extracellular matrix. Heavy menstrual bleeding (HMB), the most common symptom of UF, affects approximately 40.7% to 92.9% of women with this condition. Other common symptoms of UF include pain, pelvic pressure and urinary and gastrointestinal symptoms. Associated pain is experienced by as many as 78.8% of women with UF; its intensity varies widely depending upon the size and location of the leiomyomas.

The incidence and prevalence of UF are hard to estimate accurately. Results of 4 large epidemiologic studies performed in the United States from 1989 to 2006 (Nurses Health Study II [1989-1993], California Teachers Study [1991-2006], Uterine Fibroid Study [1996-2005] and Black Women’s Health Study [1997-2001]) showed incidence rates of 217.4 to 3,745 per 100,000 women-years. However, the Black Women’s Health Study, involving Black women exclusively, showed notably higher rates of UF than reported in trials having an underrepresentation of Black women. The estimated prevalence rates over the same time periods are similarly broad and range from 4.5% to 68.6%, depending on subject populations, region and study designs. UF most likely is not diagnosed for various reasons. For example, women often are unaware that their menstrual symptoms are abnormal and do not actively seek treatment, and there is no consensus about how best to detect the condition. Thus, true estimates of its prevalence are skewed.

The effect of UF on quality of life (QOL) often is severe, because the condition can have detrimental effects on relationships with partners and family members, activities of daily living and employment and career advancement. The heavy clinical burden of UF is accompanied by an equally large economic burden. In 2010, the estimated annual costs in the United States were as high as $34 billion; indirect costs accounted for roughly half of this total and direct costs were largely related to surgical interventions. In particular, surgical costs involved hysterectomies. From 2001 to 2005, approximately 32% of all hysterectomies performed in the United States were related to UF.

Management of UF
The main goals of UF management are relief of symptoms, reduction in size or elimination of fibroids, maintenance of fertility (in patients for whom it is a priority) and avoidance of patient harm. Various guidelines for UF treatment have been published, but opinions on optimal treatment strategies and their place in therapy are fairly diverse, partially because robust clinical data are lacking on several of the most commonly used approaches. Moreover, most published treatment guidelines were produced five to 10 years ago; they generally do not include information on recently approved medical treatments for UF symptoms.

Some treatment guidelines for symptomatic UF recommend medical management approaches for first-line therapy, with surgical approaches reserved for second- or third-line treatment. Others, depending on the location of the fibroids, advocate that symptomatic UF be managed with...
less or more invasive surgery as a first-line strategy. Among medical therapies approved in the United States, the levonorgestrel intrauterine device is one of the most commonly recommended contraceptive agents used to manage UF. Tranexamic acid, a lysine derivative with antifibrinolytic activity, is recommended for treating patients with HMB, although evidence for its use is limited. In 2021, gonadotropin-releasing hormone (GnRH) agonists were recommended by the American College of Obstetricians and Gynecologists (ACOG) for short-term treatment of HMB and as a bridge therapy prior to longer-term therapies. GnRH agonists are limited to short-term use because of a significant risk of bone loss with long-term therapy; also, these agents may induce menopausal symptoms.

The ACOG guidelines recommend hysterectomy as the definitive management of HMB and UF in women for whom fertility is not a priority and who accept the removal of their uterus. This serious surgical intervention, however, is associated with risk of morbidity and mortality. For women who want to retain their uterus and their fertility, the ACOG guidelines recommend myomectomy, a minimally invasive procedure that may result in fibroid recurrence. Other recommended alternatives include uterine artery embolization and radiofrequency ablation. Both allow uterine preservation, although their effects on reproductive health remain uncertain. Whatever treatment for UF is selected, the choice of therapy should depend upon patient preference and women should be advised about all the available treatment options and informed of the risks and benefits of each modality.

**GnRH agonists**

GnRH agonists offer a novel option for the treatment of HMB associated with UF. These medications have demonstrated a high degree of efficacy without many of the side effects associated with other oral therapies, although they must be used with hormonal “add-back” to avoid hypoestrogenic side effects and loss of bone mineral density.

The first GnRH antagonist to receive FDA approval for treating HMB associated with UF — and the first oral therapy approved for this indication — was elagolix with add-back hormonal therapy given orally twice daily (in the morning, a capsule containing elagolix 300 mg plus estradiol 1 mg/norethindrone acetate 0.5 mg; in the evening, a capsule containing only elagolix 300 mg). The FDA approval of elagolix was accompanied by a limitation-of-use statement that it should not be used for more than 24 months based on the risk of permanent bone loss. Two identical and pivotal phase 3 trials — Elaris Uterine Fibroids 1 and 2 (UF-1 and UF-2) — involved 791 premenopausal women randomly assigned 2:1:1 to receive twice-daily oral doses of elagolix 300 mg with add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg), elagolix 300 mg alone or placebo.
The primary end point (menstrual blood loss < 80 mL and reduced blood loss ≥ 50% from baseline to the last month of a six-month treatment period) was achieved by 68.5% and 76.5% of patients treated with elagolix plus add-back therapy in UF-1 and UF-2, respectively, as compared with 8.7% and 10% of women receiving placebo (both comparisons, P < .001). Women receiving elagolix alone and those given combination therapy achieved similar results.

Relugolix is the first once-daily GnRH antagonist to receive FDA approval for managing HMB associated with UF. As with elagolix, the approval was accompanied by a 24-month limitation-of-use statement. This once-daily oral formulation includes relugolix 40 mg plus estradiol 1 mg/norethindrone acetate 0.5 mg. In all, 770 premenopausal women participated in two identical phase 3 trials (LIBERTY 1 [L1] and LIBERTY 2 [L2]) to evaluate its efficacy and safety. The primary end points (menstrual blood loss < 80 mL and ≥ 50% reduction of blood loss from baseline) were similar to those of the Elaris trials, but the evaluation involved the last 35 days of the treatment period. The women were randomly assigned 1:1:1 to receive the once-daily oral combination of relugolix plus estradiol/norethindrone acetate for 24 weeks, relugolix 40-mg monotherapy for 12 weeks followed by the combination therapy for another 12 weeks (to assess a delayed add-back therapy approach), or placebo for 24 weeks. Among patients given 24-week combination therapy, the primary end point was achieved by 73% of patients in L1 and 71% of those in L2 as compared with 19% and 15%, respectively, of the placebo groups (both P < .001). Similar results were observed in the delayed add-back treatment and the 24-week combination therapy groups. Effects on bone marrow density and incidences of side effects were similar among the combination therapy and placebo groups; however, decreased bone mineral density was seen in the monotherapy group.

Conclusions

Many women with UF underestimate its consequences and the availability of viable treatments that could improve their symptoms and QOL. Available treatment options for UF include medical therapies and surgical interventions of varying invasiveness. The use of several medications and drug classes that can reduce HMB has been limited by side effects (e.g., risk of liver toxicity, downstream effects of hypoestrogenism). GnRH antagonists offer a safe, efficacious therapeutic option for UF with a limited possibility of side effects when used with add-back hormonal therapy to reduce the risks of hypoestrogenism. The once-daily oral GnRH antagonist relugolix provides the therapeu-
tic advantages of this drug class and a once-daily dosing regimen.

REFERENCES

This material is intended for use by payers, formulary committees, or other similar entities for purposes of population-based drug selection, coverage, and/or reimbursement decision making, pursuant to FD&C Act Section 502(a).

**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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• **Powerful efficacy** and **robust anatomic outcomes** across all indications as shown in 8 phase 3 clinical trials¹⁻⁸
• A broad range of indications and **dosing flexibility** across several FDA-approved indications²

• **Demonstrated safety** profile across 4 VEGF-driven retinal diseases: Wet AMD, DR, DME, and MEIRVO¹
• 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

• **10 years** of extensive real-world experience¹ and >20 million doses administered to >1.6 million eyes since launch (and counting)³
• 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® (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.
Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
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<tr>
<td>EYLEA</td>
<td>CVIVO</td>
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<tr>
<td>≥3%</td>
<td>≥3%</td>
<td>≥3%</td>
</tr>
<tr>
<td>Eye pain</td>
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<td>0%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
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<td>1%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
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<td>1%</td>
</tr>
<tr>
<td>Retinal pigment epithelum tear</td>
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<td>0%</td>
</tr>
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<td>1%</td>
<td>1%</td>
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<tr>
<td>Vitreous hemorrhage</td>
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<td>0%</td>
</tr>
<tr>
<td>Lid edema</td>
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<td>0%</td>
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<tr>
<td>Eyelid edema</td>
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<td>0%</td>
</tr>
<tr>
<td>Eyelid pain</td>
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</tbody>
</table>
| Less common adverse reactions reported in patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Table 3: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

<table>
<thead>
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<th>Adverse Reaction</th>
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<th>Baseline to Week 96</th>
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<td>≥3%</td>
<td>≥3%</td>
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<td>Intraocular pressure increased</td>
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<tr>
<td>Ocular hyperemia</td>
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<tr>
<td>Retinal detachment</td>
<td>2%</td>
<td>5%</td>
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<tr>
<td>Foreign body sensation in eyes</td>
<td>2%</td>
<td>4%</td>
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<tr>
<td>Vitreous floaters</td>
<td>1%</td>
<td>3%</td>
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<tr>
<td>Retinal pigment epithelum tear</td>
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<tr>
<td>Retinal detachment</td>
<td>0%</td>
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<td>Vitreous hemorrhage</td>
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<td>Lid edema</td>
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<td>Eyelid edema</td>
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<tr>
<td>Eyelid pain</td>
<td>0%</td>
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</tr>
</tbody>
</table>
| Less common adverse reactions reported in patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO): The data described below reflect 6 months exposure to EYLEA with a ≥7 dose in 203 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).
Although the idea of smartphones as personal health devices has become common among the general public, the integration of that idea into the formal regulatory and payment structure remains very much a work in progress.

One potential milestone could be on the horizon. Congress is considering legislation called the Access to Prescription Digital Therapeutics Act of 2022, a bipartisan bill that would establish benefit categories for certain digital therapeutics so that they could be reimbursed by Medicare, Medicaid and other public payers. Versions of the bill were introduced in both the House and Senate in March. Proponents, including the Digital Therapeutics Alliance, an industry trade group, argue it would bring much-needed clarity and legitimacy to digital therapeutics.

In the meantime, developers of prescription digital therapeutics continue to press forward. In March, the prescription digital therapeutics maker metaMe Health announced a partnership with Indegene to commercialize a new digital therapeutic to treat abdominal pain associated with irritable bowel syndrome (IBS). The smartphone app received clearance from the FDA in late 2021.

Tim Rudolphi, MBA, metaMe’s chief executive officer, told Managed Healthcare Executive that their digital therapeutic, Regulora, would have the effect of expanding access to a type of drug-free therapy for IBS-related pain. He says symptoms of IBS are mediated by a dysregulation of sensory and motility signaling between the brain and gut, leading to hypersensitivity and gut pain. Regulora administers gut-directed hypnotherapy (GDH), which aims to resolve the brain-gut “miscommunication” and thereby alleviate symptoms.

“GDH has been shown to produce positive outcomes for those living with IBS, but has previously been inconvenient for many patients, as it has required in-person visits with trained therapists,” he explains. “With Regulora, patients can access treatment privately from anywhere at any time, empowering them to improve their quality of life without hassle or fear of stigma.”

Though the app makes therapy administration simpler, the company is now focused on making sure that obtaining the app is equally streamlined. Rudolphi says if all goes according to plan, the process should look much the same as obtaining a bottle of pills from the pharmacy.

“The physician writes the prescription and sends it off to the pharmacy,” he says. “The pharmacy will adjudicate with insurance, collect payment, and issue the access code.” That access code will allow the patient to unlock the app, which patients can download from the Apple and Android app stores. The access code will work for the duration of the prescribed course of treatment, which, according to Rudolphi, is generally expected to be 12 weeks. He notes the intention is for payers to pay a one-time fee for the entire course of treatment.

Under metaMe’s multiyear deal with Indegene, the latter will use its commercialization model to conduct outreach to both physicians and patients. Indegene says it will use machine learning and artificial intelligence to identify potential patients.

Regulators’ embrace

Still, the success of products like Regulora will depend on more than patients and physicians. Digital therapeutics makers will also need to convince regulators to embrace the technology and payers to pay for it.

Andy Molnar, chief executive officer of the Digital Therapeutics Alliance, says laws such as the Access to Prescription Digital Therapeutics Act of 2022 are an important early step in that process. “The need for a benefit category and proper coding will allow for patients and providers to own their care,” Molnar said in a press release.

For his part, Rudolphi is optimistic that payers will cover Regulora. He says his company plans to launch the product later in 2022.

Jared Kaltwasser, a regular contributor to Managed Healthcare Executive, is a healthcare writer in Iowa.
Most cancers tend to have a genetic, hormonal or environmental cause, but various infections also have been identified as causing certain cancers. According to the American Cancer Society, infections are linked to about 15% to 20% of cancers worldwide. Although some cancer-causing infectious agents are limited to the developing world, many are common in the U.S.

Researchers’ understanding of the link between infectious diseases and cancer continues to evolve, but many barriers stand in the way. The number of infectious agents is nearly infinite, and isolating ones that might play a causative role in the disease is challenging. A cancer may take many years, sometimes decades, to develop after an infection. Tracing it back to infection is a research challenge and costly.

Warren A. Chow, M.D., FACP, associate director for clinical sciences at the University of California Irvine Chao Family Comprehensive Cancer Center, notes there haven’t been any recent discoveries concerning cancer-causing infectious agents in the past five to 10 years, but that doesn’t mean there won’t be more in the future. In fact, Chow says he expects that as research continues, new links between infectious disease and cancer will come to light.

The National Cancer Institute (NCI) lists 10 infectious agents as having the potential to cause cancer or markedly increase the risk of its occurring.

**Epstein-Barr virus (EBV).** A type of herpes virus, Epstein-Barr causes certain types of lymphoma and cancers of the nose and throat.

**Hepatitis B virus and hepatitis C virus.** Chronic infection with hepatitis B or C virus can cause liver cancer.

**HIV.** HIV does not appear to be a direct cause of cancer but if left untreated it weakens the immune system and makes infections, some of which are linked to cancer, more likely. According to NCI, people infected with HIV are at increased risk of Kaposi sarcoma, lymphoma (including non-Hodgkin lymphoma and Hodgkin disease) and cancers of the anus, cervix, throat, liver and lung.

**Human papillomavirus (HPV).** Infection with the high-risk types of HPV causes nearly all cervical cancers and most anal cancers. HPV infection also causes many oropharyngeal, vaginal, vulvar and penile cancers.

**Human T-cell leukemia/lymphoma virus type 1.** Human T-cell leukemia/lymphoma virus type 1 causes adult T-cell leukemia/lymphoma, an aggressive variety of non-Hodgkin lymphoma.

**Kaposi sarcoma-associated herpesvirus.** Also known as human herpesvirus-8, Kaposi sarcoma-associated herpesvirus causes Kaposi sarcoma, a cancer that forms in the lining of the blood and lymph vessels. In sub-Saharan Africa and some parts of Central and South America, the virus is spread by contact with saliva among family members. In the U.S. and northern Europe, it is sexually transmitted.

**Merkel cell polyomavirus.** Merkel cell polyomavirus causes Merkel cell carcinoma, a rare type of skin cancer. The risk is increased in older people and in younger adults with suppressed immune systems.

**Helicobacter pylori.** Helicobacter pylori, a bacterium, causes noncardiac gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma, a type of lymphoma that arises in the stomach lining.

**Opisthorchis viverrini.** Opisthorchis viverrini is a parasitic flatworm found in Southeast Asia that can cause cholangiocarcinoma (bile duct cancer).

**Schistosoma haematobium.** Schistosoma haematobium is a parasitic flatworm like opisthor-
chis viverrine. It lives in freshwater snails in Africa and the Middle East and can cause bladder cancer.

**How it happens**

Darshak Sanghavi, M.D., chief of pediatric cardiology at the University of Massachusetts Medical School and global chief medical officer at Babylon, a digital-first health service provider, notes that although it’s not completely understood how infectious agents cause cancer, some infections can result in DNA damage that causes the runaway cell growth that characterizes the disease. Some infections can result in long-term inflammation and the inflammatory factors involved may lead to errors during cell replication, resulting in cancer-causing mutations.

Others may suppress a person’s immune system, which normally may help keep cancer development in check.

Sean Marchese, M.S., RN, has a background in oncology clinical trials and over 15 years of direct patient care experience working at the Mesothelioma Center in Orlando, Florida. He says the best-understood pathway from infection to cancer development is inflammation. The damaged cells in inflamed tissues eventually lose essential parts of their DNA and spiral out of control until they form tumors in the area.

“The more insidious ways infections cause cancer is through direct genetic manipulation by certain viruses,” he says. “Viruses can manipulate the body’s cells and DNA mechanisms to create proteins that help the virus multiply and infect more cells. By altering our genes, viruses such as the hepatitis virus, HPV, HIV, and EBV can cause cancers in the blood, liver, pelvis, etc.”

Chow notes that the first virus to be identified as causing cancer was discovered in chickens (by Peyton Rous in 1910. He was awarded a Nobel Prize for the discovery in 1966). Although some viruses may cause cancer by directly affecting DNA, Chow says bacterial infections are likely to do so by stirring up inflammation and altering the immune system.

**Vaccination as cancer prevention**

Cancer prevention is often viewed as involving tobacco cessation, dietary changes, removing carcinogenic products from the market and so on. But vaccination against cancer-causing infections also belongs on that list.

Among the best-described correlations between a viral infection and malignancy is that of the human papillomavirus, notes Javeed Siddiqui, M.D., M.P.H., co-founder and chief medical officer of TeleMed2U, a specialist telemedicine company. Siddiqui specializes in infectious diseases, especially hepatitis and HIV.

“There are over 200 different serotypes of the human papillomavirus; however, we know that certain ones are clearly associated with a higher rate of cancer formation,” he says. “Specifically, human papillomavirus serotypes 6, 11, 16 and 18 are strongly associated with cervical cancer. In addition, these serotypes can also be associated with vaginal, vulvar, anal and oropharyngeal cancers.”

The CDC recommends that the two-shot HPV vaccine be given routinely at age 11 or 12 (the shots can be started at age 9). Older people can get the vaccine if they don’t think they were adequately vaccinated when they were younger.

Hepatitis B vaccination also works against cancer. The vaccine is recommended for all infants, all children or adolescents younger than 19 years who have not been vaccinated, all adults aged 19 through 59 years, and adults aged 60 or older with risk factors for hepatitis B infection.

Management of HIV is another avenue for combating cancer. “A persistent degree of immunosuppression and a CD4 count less than 100, or even a more profound degree of immune suppression resulting from a CD4 count less than 50, can then give rise to Kaposi sarcoma through exposure to human herpesvirus-8,” Siddiqui says. “This is a clearly established disease process and another example of a clear link between an infectious diseases pathogen, specifically a virus, and the emergence of a malignancy.”

“If you control the HIV-1 infection with antiretroviral therapy,” says Chow, “you actually control the Kaposi sarcoma that is a result of human herpesvirus-8. You get the HIV RNA titer down, the CD4 cell count up, and the Kaposi sarcoma often regresses.”

Infectious diseases changes are occurring all the time. Look no further than COVID-19. Meanwhile, Siddiqui points out, so is our understanding of cancer. “There will continue to be intersections and associations between infectious disease and oncology,” he says. “It would be naive to think that there will not be new agents and new diseases that are involved or discovered at this intersection.”

**Keith Loria** is a healthcare writer in the Washington, D.C., area.
Scott Gottlieb, M.D., former FDA commissioner and Asembia keynote speaker, was sanguine about the future course of the COVID-19 pandemic and biosimilars. He expressed concern, though, that the CMS Aduhelm (aducanumab) coverage decision had set a bad precedent.

In a fireside chat format with Adam J. Fein, a well-known drug industry and pricing expert, Gottlieb commented on a range of subjects, from predictions about the pandemic’s course to the CDC’s shortcomings to biosimilars to drug rebates. Some of his sharpest words were directed at CMS’ decision to limit coverage of Aduhelm, which Gottlieb said may set a precedent for limited coverage for other drugs given accelerated approval by the FDA.

As FDA commissioner, Gottlieb said he worked with the then-CMS Administrator Seema Verma to successfully push back on plans by Massachusetts’ Medicaid program to limit coverage of drugs that had received accelerated approval. “Now CMS has opened the barn door to this kind of policy making,” said Gottlieb, “you are going to see state Medicaid plans follow suit and you are going to eventually see commercial plans and they are going to use accelerated approval as the sole basis for not putting a drug on formulary.”

Gottlieb sketched a picture of the pandemic settling into a seasonal pattern resembling that for flu. But one of the big questions, he said, is whether the dominant form of the coronavirus that causes COVID-19 will remain so in the omicron lineage or emerge from a divergent evolutionary path.

Gottlieb’s 2021 book, “Uncontrolled Spread: Why COVID-19 Crushed Us and How We Can Defeat the Next Pandemic,” was critical of the CDC’s response to the pandemic, and Gottlieb repeated some of that criticism at the Asembia meeting. He said the agency was organized to develop tests for new diseases in a “highly sequential process” that was overwhelmed by the pandemic. He added that the agency was inept in following its own, flawed process: “They literally contaminated their own lab.” He said he favors orienting the agency toward national security organization and perhaps delegating some of its prevention efforts to other agencies.

—Peter Wohrwein

Gottlieb sees bad precedent in Aduhelm coverage system, a need for major changes at CDC

Fein, Long say PBMs, payers and large hospitals are tightening their grip on specialty pharmacy

Pharmacy benefit managers (PBMs) continue to dominate specialty dispensing and payer control is challenging patient access to drugs, Adam J. Fein, Ph.D., CEO, Drug Channels Institute, and Doug Long, vice president, industry relations, IQVIA, told a large audience at a general session of the Asembia meeting.

Fein said the top three specialty pharmacies by revenue in 2021 were the three large PBMs: CVS Caremark (owned by CVS Health), Express Scripts (owned by Cigna) and OptumRx (owned by UnitedHealth Group). Payers are not only limiting where patients can go, but they are often sending patients to the specialty pharmacy owned by their PBM, he said.

The 340B program (a federal
Continued on page 64
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Continued from page 62

program that gives some hospitals discounted drug prices) is another big driver in specialty pharmacy, Fein said. CVS Health, Express Scripts and OptumRx, along with Walgreens and Walmart, hold the majority (73%) of 340B contract pharmacy relationships. Fein said the program has recently faced a massive change, though, as 16 drug manufacturers have pulled back from offering 340B discounted pricing to contract pharmacy networks.

Fein discussed vertical integration. Hospitals buying up physician practices had “accelerated more than you might think,” he said, and hospitals and health systems have started to steer patients to their own specialty pharmacies.

Long reminded the audience of the growing market share of specialty medicines. In February 2022, specialty drugs accounted for 49.9% of drug sales, he said. He also discussed slower spending growth in certain therapeutic areas, such as multiple sclerosis and HIV, because generics and biosimilars have come on the market. Long said biosimilars are beginning to have an effect on the oncology drug spend. —Laura Joszt

Walgreens, TailorMed team up to deal with prescription abandonment

Getting a prescription is one thing, filling it is another. And a large percentage of patients — the proportion varies with the price of the medication — don’t fill their prescriptions.

Sarah Freedman, a senior manager of specialty pharmacy operations at Walgreens, and Sruilik Dvorsky, CEO of TailorMed, discussed the problem of “prescription abandonment” during a session at the 2022 Asembia Specialty Pharmacy Summit in Las Vegas.

TailorMed is a self-described financial navigation company, founded in 2018 by Dvorsky. The company’s platform uses information about the patient and their prescriptions to connect them to financial assistance programs of various kinds, such as drug coupons and government assistance programs. Dvorsky told the Asembia audience that the platform now includes about 5,000 programs that might help patients with the financial aspects of their healthcare.

TailorMed signed a contract with Walgreens in June 2021. According to Dvorsky, the company’s software is being used in 350 of Walgreens’ specialty pharmacies.

Freedman said that identifying financial assistance for patients is an important but time-consuming process for pharmacists. She noted that TailorMed’s technology should help free up time for pharmacists to explain some of the financial assistance programs to patients rather than having to deal with some of the tasks involved. —Peter Wehrwein

Make — and keep — it simple, say Amazon Pharmacy executives

The shift to online pharmacy is a golden opportunity to reorient pharmacy services so people can see prices and get medications conveniently, panelists at a session on e-commerce and pharmacy agreed. The Amazon Pharmacy executives on the panel referred several times to the importance of keeping the online experience simple for customers.

The upbeat session about e-commerce and pharmacy came a day after Department of Justice officials issued a press release announcing that PillPack had agreed to pay a $5.79 million penalty for overbilling Medicare and Medicaid for insulin. Amazon acquired PillPack in 2018.

During the Asembia session, Geoff Swindle, chief business officer, Amazon Pharmacy, discussed the partnership that Amazon Pharmacy has with Prime Therapeutics, a pharmacy benefit manager based in the Minneapolis area that manages pharmacy benefits for Blues plans. He said the company has made it easy for Prime members to easily onboard to Amazon Pharmacy, pulled in medication histories and displayed pricing so out-of-pocket costs are clear.

Laura Jensen, vice president of commercial markets, pharmacy, pharma, also invoked simplicity as a central element to an Amazon-wide philosophy: “When we talk to our customers about what they are looking from us, they are really looking for us to create a pharmacy experience that is simple, that is easy for them to understand and that feels and looks like any other experience on Amazon.”

Aimee Corso, marketing leader at Amazon Pharmacy, moderated the session. —Peter Wehrwein
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