THE RNA MOMENT

Treatments and vaccines using and targeting ribonucleic acid have taken center stage.

Also

CHRONIC DISEASE
Seeing LDL cholesterol in a new light

FORMULARY DEVELOPMENT
A conversation with Ken Paulus, CEO of Prime Therapeutics

CONFERENCE COVERAGE
AMCP Nexus 2021
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.

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).

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON
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).


Please see Brief Summary of full Prescribing Information on the following page.
Eyelid edema 1% 2% 2% 3%
Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Retinal detachment <1% <1% 1% 1%
Corneal edema 1% 1% 1% 1%

Intraocular pressure increased 5% 7% 7% 11%
Vitreous floaters 6% 7% 8% 10%

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

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

Table 2: Most Common Adverse Reactions (≥3%) in RVO Studies

Table 3: Most Common Adverse Reactions (≥3%) in DME Studies

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

Regeneron is a registered trademark of Regeneron Pharmaceuticals, Inc.

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

Intraocular pressure and the perfusion of the optic nerve head should be monitored and reported any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (See Warnings and Precautions (5.2).)

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment/management of patients with:

4.2 Intraocular Pressure

4.3 Hypersensitivity

5.3 Thromboembolic Events

Regeneron Pharmaceuticals, Inc.

5.4 Pregnancy

5.5 Breastfeeding

Regeneron Pharmaceuticals, Inc.

2.3 Clinical Trials Experience

EYELID EDema 1% 2% 2% 3%
Less common serious adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, and endophthalmitis.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across the studies.

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RNA steps into the limelight

In a trivia contest, most of us could probably answer a few questions about DNA. That it has that iconic double-helix shape, discovered by Watson and Crick (bonus points if you also mention Rosalind Franklin, who is finally getting some of the credit she deserves). That it is the stuff of which genes are made. Maybe a few smarties could name DNA’s four nucleotides — adenine, cytosine, guanine, and thymine — or at least some of their initials.

But RNA? It would most likely have been greeted with blank stares or nervous, unknowing laughter. Pigeonholed as the mere translator of DNA, the go-between from DNA to the assemblage of proteins that DNA codes for, RNA has never had much star power or name recognition.

Like so much else that has changed in 2021. The Pfizer and Moderna COVID-19 vaccines are RNA based. They consist of snippets of RNA that carry the instructions for making the proteins on the surface of the SARS-CoV-2 virus. Those are the proteins that give the virus that now-familiar spikey appearance that is reminiscent of a medieval mace. RNA vaccines are an ingenious way of delivering an antigen that trains the immune system to recognize a virus without having to deliver the antigen itself.

But as we discuss in this month’s cover story, RNA has become an exciting platform for drug discovery and development of all kinds, not just vaccines. The fact that RNA is DNA’s translator presents an opportunity for blocking the production of abnormal proteins “upstream” without the drawbacks of tinkering DNA and the genetic code. “Targeting RNA offers the benefit of eliminating the effect of a mutation close to the source yet without a permanent change to the hereditary information,” said Tom Misteli, Ph.D., director of the Center for Cancer Research at the National Cancer Institute, in an interview for our cover story.

The pace of discovery in American healthcare is breathtaking — and something to be grateful for during this month of giving thanks. RNA therapeutics are an example of the brilliant innovation that can occur through the combination of science and enterprise.
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Manager Healthcare Executive (ISSN 1533-9300, Digital ISSN 2150-7120) is published monthly by MJH Life Sciences™, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Subscription rates: 1 year $99.00, 2 years $145.00 in the United States & Possessions; 1 year $122.00, 2 years $173.25 in Canada and Mexico; 1 year $192.00, 2 years $295.00 in all other countries. For air-expedited service, include an additional $87.00 per order annually. Single copies (prepaid only): $9.00 in the United States, $23.00 in all other countries. Back issues, if available: $15.00 in the U.S., $17.00 in all other countries. Include $6.00 per order plus $3 per additional copy for U.S. postage and handling. If shipping outside the U.S., include an additional $10 per order plus $3 per additional copy.

Periodicals postage paid at Trenton, NJ 08650 and additional mailing offices. POSTMASTER: Please send address changes to Managed Healthcare Executive, P.O. Box 1567, Cranbury N.J. 08512-0156. Canadian GST number: R14013736T01. PUBLICATIONS MAIL AGREEMENT NO. 40002008. Return Undeliverable Canadian Addresses to: Nexis Global Solutions, P.O. Box 25142, London, ON N6C 0B2, CANADA.

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NOW AVAILABLE

For the treatment of adults with schizophrenia or bipolar I disorder

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Most common adverse reactions observed in clinical trials were:

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

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

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

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

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

Please see the Brief Summary of Full Prescribing Information, including Boxed Warning, for LYBALVI on the following pages.
LYBALVI® (olanzapine and samidorphan) tablets, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
(For complete details, see full Prescribing Information)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

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

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

If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

WARNINGS AND PRECAUTIONS
Increased Mortality in Elderly Patients with Dementia-Related Psychosis:
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than in placebo-treated patients (3.5% vs 1.5%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death or infectious e.g., pneumonia) in nature. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis:
Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with olanzapine compared to patients treated with placebo. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

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

Vulnerability to Life-Threatening Opioid Overdose
Risk of Opioid Overdose from Attempts to Overcome Samidorphan Blockade:
LYBALVI contains samidorphan, an opioid antagonist. Attempting to overcome LYBALVI’s opioid blockade with high or repeated doses of exogenous opioids (e.g., because of ineffective analgesia or opioid withdrawal symptoms) could lead to life-threatening or fatal opioid intoxication (e.g., respiratory arrest, circulatory collapse), particularly if LYBALVI therapy is interrupted or discontinued, subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If signs and symptoms of tardive dyskinesia appear in a patient on LYBALVI, drug discontinuation should be considered. However, some patients may require treatment with LYBALVI despite the presence of the syndrome.

Orthostatic Hypotension and Syncope:
Orthostatic hypotension and syncope are potentially a problem for LYBALVI treated patients. In the 24-week, olanzapine-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension were less than 2% in LYBALVI- and placebo-, and olanzapine-treated patients. In the 24-week, olanzapine-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension in LYBALVI-treated patients were 3.7%, compared to 0.4% in olanzapine-treated patients.
Monitor orthostatic vital signs in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medications or ONS depressants, patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease). LYBALVI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

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

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

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

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue LYBALVI in patients with severe neutropenia (absolute neutrophil count <1000/mm$^3$) and follow their WBC until recovery.

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

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

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

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

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

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

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D$_2$ receptors, olanzapine, a component of LYBALVI, elevates prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

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

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

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

**ADVERSE REACTIONS**

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

**Adverse Reactions in Patients with Schizophrenia:**

**Patient Exposure**

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

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

The most common adverse reactions (incidence of at least 5% of patients exposed to LYBALVI and greater than twice the rate of placebo) are weight increase, somnolence, dry mouth, and headache.

Adverse reactions associated with the use of LYBALVI (incidence of 2% or greater and greater than in placebo-treated patients) are shown in Table 1.

| Table 1: Adverse Reactions Reported in ≥2% of LYBALVI-Treated Patients and Greater than Placebo in a 4-Week Schizophrenia Trial |
|-------------|-----------------|-----------------|
| Adverse Reaction | Placebo (N=134) % | LYBALVI (10 mg, 20 mg, 10 mg) (N=134) % |
| Weight increased | 3 | 19 |
| Somnolence | 2 | 9 |
| Dry mouth | 1 | 7 |
| Headache | 3 | 6 |
| Blood insulin increased | 1 | 3 |
| Sedation | 0 | 2 |
| Dizziness | 1 | 2 |
| Neutrophil count decreased | 0 | 2 |

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

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

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

Adverse reactions that led to LYBALVI treatment discontinuation in more than one patient include somnolence (2%), weight increased (2%), and nausea (2%).

Glycosylated hemoglobin increased (1%), schizophrenia (1%), and liver function test abnormal (1%).

**Hyperglycemia:** Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of
the 2 highest serum concentrations was 15.0 mg/dL. Hyperglycemia, as defined by fasting glucose ≥126 mg/dL, has been observed in patients treated with LYBALVI. In the 4-week placebo-controlled trial in adult patients with schizophrenia, shifts in fasting glucose from normal to high occurred in 4% of patients treated with LYBALVI, 1% of patients treated with olanzapine, and no patients treated with placebo.

In the 24-week olanzapine-controlled trial, patients treated with LYBALVI were more likely to experience abnormal shifts in glycemic parameters than patients treated with olanzapine (Table 2).

### Table 2: Changes in Glycemic Parameters in a 24-Week Trial of Patients with Schizophrenia

<table>
<thead>
<tr>
<th>Proportion of Patients with Shifts, % (n/N)*</th>
<th>LYBALVI</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>12 (26/223)</td>
<td>8 (18/219)</td>
</tr>
<tr>
<td>Impaired (≥100 mg/dL and &lt;105 mg/dL) to High (≥126 mg/dL)</td>
<td>24 (9/38)</td>
<td>11 (5/47)</td>
</tr>
<tr>
<td>Increase ≥10 mg/dL</td>
<td>66 (174/265)</td>
<td>57 (154/270)</td>
</tr>
<tr>
<td>Hemoglobin A1c Normal (&lt;5.7%) to Impaired (≥5.7% and ≥8.5%)</td>
<td>42 (86/204)</td>
<td>35 (68/197)</td>
</tr>
<tr>
<td>Normal to High (≥5.7% and ≥6.5%)</td>
<td>0.5 (1/204)</td>
<td>1.5 (3/197)</td>
</tr>
<tr>
<td>Impaired (≥5.7% and ≥8.5%) to High (≥6.5%)</td>
<td>9.5 (6/63)</td>
<td>9.2 (17/176)</td>
</tr>
</tbody>
</table>

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

### Drug Interactions

### Effects of Other Drugs on LYBALVI: Table 3 describes clinically significant drug interactions where the concomitant use of other drugs affects LYBALVI.

#### Table 3: Effects of Other Drugs on LYBALVI

### Strong CYP3A4 Inducer

- **Clinical Implication:** Coadministration of LYBALVI with a strong CYP3A4 inducer decreases AUC of olanzapine and samidorphan which may reduce LYBALVI efficacy.
- **Prevention or Management:** Concomitant use of LYBALVI with strong CYP3A4 inducers is not recommended.

### Strong CYP1A2 Inhibitor

- **Clinical Implication:** Concomitant use of LYBALVI with a strong CYP1A2 inhibitor increases olanzapine AUC and Cmax, which may increase risk of LYBALVI adverse reactions.
- **Prevention or Management:** Consider reducing the dosage of the olanzapine component in LYBALVI when used concomitantly with strong CYP1A2 inhibitors.

### CYP1A2 Inducer

- **Clinical Implication:** Concomitant use of LYBALVI with CYP1A2 inducers decreases olanzapine exposure, which may reduce LYBALVI efficacy.
There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including LYBALVI, during pregnancy. There were no adverse effects on embryofetal development at doses of olanzapine and samidorphan that are approximately 1 and 80 times, respectively, the MRHD based on AUC.

Olanzapine

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

Samidorphan

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

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease–Associated Maternal and/or Embryofetal Risk

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

Fetal/Neonatal Risks

Extrapyramidal and/or withdrawal symptoms, including agitation, hyperventilation, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including the olanzapine component of LYBALVI, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

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

Animal Data

LYBALVI

Olanzapine and samidorphan were orally administered to pregnant rats during the period of organogenesis at doses of 0.5/10, 2.5/50, 6/200, and 0/200 mg/kg/day (olanzapine/samidorphan) which are approximately <1/10 times to 6/486 times the MRHD of 20 mg/10 mg olanzapine/samidorphan, respectively, based on AUC. Maternal toxicity consisting of decreased body weight and food consumption was observed at all dose levels. Administration of samidorphan alone (200 mg/kg/day) and 6/200 mg/kg/day olanzapine/samidorphan decreased mean fetal body weights, increased litter incidence of bent ribs and bent scapula; however, the incidence of bent scapula and bent ribs was not increased when samidorphan was administered in combination with olanzapine compared to the incidence with samidorphan alone. Administration of a combination of olanzapine/samidorphan at 6/200 mg/kg/day also increased resorptions and post-implantation loss, with correlating lower mean viable fetuses and litter size. The no observed adverse effect level (NOAEL) for embryofetal development is 2/50 mg/kg/day, which is approximately 1/80 times the MRHD of 20 mg/10 mg olanzapine/samidorphan respectively, based on AUC.
Olanzapine was orally administered to pregnant rats and rabbits during the period of organogenesis at doses up to 18 mg/kg/day in rats and at doses up to 30 mg/kg/day in rabbits (9 times and 30 times the MRHD of 20 mg/day based on mg/m² body surface area, respectively), and no evidence of malformations was observed. In an oral rat embryofetal developmental toxicity study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD based on mg/m² body surface area). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD based on mg/m² body surface area). In an oral rabbit embryofetal developmental toxicity study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of olanzapine at 30 mg/kg/day (30 times the MRHD based on mg/m² body surface area).

Samidorphan was orally administered to pregnant rats during the period of organogenesis at doses of 25, 100, and 300 mg/kg/day, which are approximately 29 to 742 times the MRHD of 10 mg/day based on AUC. Samidorphan was associated with an increased incidence of skeletal variations (unossified sternebrae and bent ribs) at maternally toxic doses of ≥100 mg/kg/day, and skeletal malformations (bent or misshaped forelimbs, hindlimbs, and/or scapula) at 300 mg/kg/day which are ≥246 and 742 times the MRHD based on AUC, respectively. The NOAEL for embryofetal development is 25 mg/kg/day, which is approximately 29 times the MRHD based on AUC.

Olanzapine and samidorphan were orally administered to pregnant rats during the period of organogenesis at doses of 10, 30, and 50 mg/kg/day, which are up to approximately 143 times the MRHD based on AUC. Samidorphan was orally administered to pregnant rats during pregnancy and lactation at doses of 10, 30, or 100 mg/kg/day, which are approximately 7 to 188 times the MRHD based on AUC. Reduced pup survival, lower birth weights, and decreased pup body weight gains were observed at 100 mg/kg/day, which is 188 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 36 times the MRHD based on AUC. There were no adverse effects on pup developmental landmarks, learning, memory, reflexes, or fertility.

**Lactation**

**Risk Summary:** Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There is no information on the effects of olanzapine on milk production. There are no data on the presence of samidorphan or the combination of olanzapine and samidorphan in human milk. In animal studies, olanzapine was detected in the plasma of nursing pups, which is likely due to the presence of samidorphan in milk. Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements).

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

**Females and Males of Reproductive Potential**

**Infertility**

Based on the pharmacologic action of olanzapine (D2 antagonism), treatment with LYBALVI may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

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

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

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

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

- In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine, compared to patients treated with placebo.
- In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1,184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than in placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, leukopenia, increased weight, abnormal speech, open mouth and visual hallucinations.

The rate of discontinuation due to adverse reactions was greater with olanzapine than with placebo (13% vs 7%).

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

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

**Renal Impairment:** Plasma exposure to olanzapine and samidorphan was higher in patients with severe renal impairment (eGFR 10 to 29 mL/minute/1.73 m²) compared to those with normal renal function. No dose adjustment of LYBALVI is needed in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²), or severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²).

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

**Overdose**

**Human Experience:** There is limited clinical experience with overdose with LYBALVI.

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-888-238-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**Pfizer COUNSELING INFORMATION**

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

This Brief Summary is based on LYBALVI full Prescribing Information (revised: May 2021).

Distributed by: Alkermes, Inc.

852 Winter Street
Watertown, MA 02471-1420

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Mission

Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights and strategies to pursue value-driven solutions.
Drugs that the FDA has approved on its fast-track accelerated approval basis are making up an increasingly larger share of Medicaid spending on pharmaceuticals, according to a study published recently in *JAMA Health Forum*, and some experts are suggesting that Medicaid payments be adjusted to account for their unproven clinical value.

Rachel E. Sachs, J.D., M.P.H., an associate professor at Washington University in St. Louis School of Law, and her colleague reported in *JAMA Health Forum* in October that drugs approved on the accelerated basis accounted for less than half a percentage point (0.2% to 0.4%) of state Medicaid prescriptions. But when it came to spending, they accounted for 6.4% ($2.2 billion of $34.6 billion) of the net spending in 2015, a proportion that increased to 9.1% ($2.5 billion of $27.6 billion) in 2018.

Accelerated approval of drugs started in 1992. As the name suggests, it is designed to speed up the FDA approval process so drugs with major health benefits will be available to patients sooner. To that end, the clinical trial results that the agency considers for drugs designated for accelerated approval often use surrogate end points — a lab value or other measurement that is viewed as a reliable proxy for a clinical outcome, such as prevention of heart attack or stroke.

But Sachs and her co-investigators — and others — are concerned about an approval process that depends so heavily on a surrogate end point because they can fall short of being proxies for favorable outcomes. When they do, that means Medicaid programs and other payers have paid for drugs approved on an accelerated basis that haven’t benefited patients as expected. Sachs and her co-authors cite the example of Makena (hydroxyprogesterone caproate injection), a synthetic hormone that received approval in 2011 based on its ability to reduce the risk of recurrent preterm birth, a surrogate end point for improved neonatal outcomes. But in 2019, a confirmatory trial failed to reproduce these findings. In October 2020, the FDA proposed withdrawing the approval. Sachs and her colleagues estimate that between 2012 and 2019, state Medicaid programs spent an average of $118 million per year on Makena “while seemingly achieving little or no therapeutic benefit for patients.”

High-priced cancer treatment drugs represent a growing proportion of drugs or drug indications approved on an accelerated basis. Recently, less-than-favorable postmarketing data have resulted in drug manufacturers pulling back on indications that had the FDA’s accelerated approval blessing. Earlier this year, Bristol Myers Squibb withdrew the hepatocellular carcinoma indication for Opdivo (nivolumab), Merck withdrew the metastatic gastric cancer indication for Keytruda (pembrolizumab) and Genentech withdrew the metastatic triple-negative breast cancer indication for Tecentriq (atezolizumab).

Some experts believe the FDA should be more selective about approving drugs based on surrogate end points. Others have suggested that payers could develop payment policies that would reflect the uncertainty of the clinical value of the accelerated approval drugs until there’s solid evidence from confirmatory trials and postmarketing data. Sachs and her colleagues mention a recommendation made by the Medicaid and CHIP Payment and Access Commission (MACPAC) earlier this year. By law, state Medicaid programs get hefty rebates from drug manufacturers. MACPAC, a group of outside experts appointed to advise Congress on Medicaid policies, suggested raising the rebate level on accelerated approval drugs so it is higher than the rebates for fully approved drugs.

— Denise Myshko
Federal drug price negotiation is popular — even among Republicans

Having CMS negotiate drug prices is a policy favored by President Joe Biden and many Democrats, and it is a prominent feature of H.R. 3, also known as the Elijah Cummings Lower Drug Costs Now Act.

But according to a recent Kaiser Family Foundation tracking poll, a majority of people who identify as Republicans (76%) also favor the federal government negotiating drug prices with drug companies. Not surprisingly, the notion is even more popular among Democrats (91% in favor), with independents falling in between (85% in favor) the Republicans and Democrats. The poll was conducted from Sept. 23 to Oct. 4 and included just over 1,400 respondents.

Drugmakers and other groups are vigorously opposed to federal government negotiation of drug prices and are lobbying against H.R. 3 for a variety of reasons. One that is often voiced is that price negotiation would stifle innovation and the development of therapies to manage and cure disease. A large majority of the respondents to the Kaiser poll don’t have much stock in that argument. They were asked which comes closer to their view “that even if U.S. prices were lower, drug companies would still make enough money to invest in the research needed to develop new drugs” or “drug companies need to charge high prices ... to fund the innovative research necessary for developing new drugs.” Most (93%) picked the former, including 90% of Republicans, and only 6% picked the latter. Of course, the exact wording to questions like that can make a significant difference in how people respond.

Drugmakers and their allies who don’t want federal government negotiation of Medicare prices may take some solace in the attitude toward Biden and congressional Democrats revealed by the Kaiser survey. Less than half of the respondents indicated that they have confidence in either Biden (46%) or the Democrats (48%) to do the right thing on drug prices. But confidence was even lower in congressional Republicans, with only one-third (33%) believing they will do the right thing.

— Peter Wehrwein

Investors bet big on digital health

Investor funding for digital healthcare ventures during the first three quarters of 2021 has already far outpaced last year’s levels, surpassing $20 billion for the first time, according to Rock Health, a venture capital firm that specializes in health startups.

The COVID-19 pandemic has fueled demand for digital care, and last year was the first time funding in the sector topped $10 billion, reaching $14.6 billion, according to Rock Health. This year, the sector has already attracted $21.3 billion in investments during the first three quarters of the year, with the largest share of funding going toward research and development, at $4.7 billion, and on-demand healthcare and treatment of diseases, each of which topped $3 billion.

Among clinical indications, mental health was the clear winner, bringing in more than $3 billion in investments. Investors are also plowing money into companies focused on women’s health, such as menopause support and tailored behavioral healthcare. Another growth area is digital health that aimed at closing the gaps that lead to healthcare disparities.

“Investors and entrepreneurs are betting on strong, consistent growth in the adoption of healthcare innovation, and these expectations are materializing in increased funding patterns across all stages,” said the Rock Health report.

— Susan Ladika

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- Cross-specialty feedback for multidisciplinary approaches to treatment and guidelines

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

**IMPORTANT SAFETY INFORMATION**

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

**WARNINGS AND PRECAUTIONS**

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

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

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
IN A CHRONIC SYSTEMIC DISEASE...

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

Itch relief after the first dose (as measured at Week 2) and skin clearance sustained at 1 year in adults taking DUPIXENT + TCS

Adult safety profile across 52 weeks generally consistent with Week 16

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

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

TRIAL RESULTS: The primary endpoint in Trials 3 and 6 was change from baseline in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and ≥2-point improvement at Week 16 (39% of adults treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 3, P<0.0001; and 24% of adolescents treated with DUPIXENT vs 2% with placebo in Trial 6, P<0.001). In Trial 8, the primary endpoint was change from baseline in the proportion of subjects with an IGA 0 or 1 at Week 16 (39% of children ≥30 kg treated with DUPIXENT + TCS vs 19% 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 72% at Week 16 (improvement of ≥75%: 60% of adults treated with DUPIXENT + TCS vs 23% with placebo + TCS in Trial 3, P<0.001; 42% of adolescents treated with DUPIXENT vs 8% with placebo in Trial 6, P<0.001; 75% of children ≥30 kg treated with DUPIXENT + TCS vs 26% with placebo + TCS, and 75% of children <30 kg treated with DUPIXENT + TCS vs 28% with placebo + TCS in Trial 8); and itch reduction defined by ≥4-point improvement in the Peak Pruritus NRS at Week 16 (59% of adults treated with DUPIXENT + TCS vs 20% with placebo + TCS in Trial 3, P<0.0001; 37% of adolescents treated with DUPIXENT vs 5% with placebo in Trial 6, P<0.001; 63% of children ≥30 kg treated with DUPIXENT + TCS vs 13% with placebo + TCS, and 54% of children <30 kg treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 8). Trial 3 also assessed endpoints at Week 52. IGA: 36% of adults treated with DUPIXENT + TCS vs 13% with placebo + TCS; EASI-72: 65% 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 Trial 3, improvement was seen as early as at Week 2, with EASI-72 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<0.0002).

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

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

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

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

SANOFI GENZYME 🎉

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REGENERON

DUP.21.06.0315
SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

Please see additional Important Safety Information below.

TRIAL DESIGNS: A total of 251 adolescents in Trial 6, 367 children (6-11 years of age) in Trial 8 (16 weeks each), and 421 adults in Trial 3 (52 weeks) with moderate-to-severe atopic dermatitis inadequately controlled with topical prescription therapies were randomized to DUPIXENT or placebo. All patients in Trials 3 and 8 received concomitant TCS. All DUPIXENT-treated adults and adolescents ≥60 kg received 300 mg Q2W after a 600 mg loading dose. Adolescents <60 kg but ≥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 Trials 3 and 6, patients had moderate-to-severe disease, with an IGA score ≥3 (overall lesion severity score of 0 to 4), an EASI score ≥16 on a scale of 0 to 72, and BSA involvement ≥15%. At baseline, 50% of adults and 46% of adolescents had an IGA score of 3 (moderate), 50% of adults and 54% of adolescents had an IGA of 4 (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 10.1-5

IMPORTANT SAFETY INFORMATION (cont’d)

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

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

USE IN SPECIFIC POPULATIONS

• Pregnancy: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Healthcare providers and patients may call 1-877-511-8972 or go to https://mothersandbaby.org/ongoing-study/dupixent/ to enroll in or obtain information about the registry. Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.

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

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

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

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

 Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see Adverse Reactions (6.1)]. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.5 Reduction of Corticosteroid Dosage

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

5.6 Patients with Comorbid Asthma

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 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 antihelminthic treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS). A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis. Trials 1, 2, and 3 (Trials 1, 2, and 3) compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52. Weeks 0 to 16 (Trials 1, 2, and 3) and Weeks 0 to 16 (Trials 1, 2, and 4) through Week 16. In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapy</th>
<th>DUPIXENT + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>51 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Keratitis*</td>
<td>51 (10)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Keratitis*</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection†</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Pooled analysis of Trials 1, 2, and 4.

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

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

8.1 Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage patients to register their pregnancy [see Pregnancy (14.1)].

8.2 Nursing Mothers

DUPIXENT is transmitted into human milk in high concentration from maternal serum. The effect of DUPIXENT in human milk on the breastfed child from DUPIXENT or from the comparator groups during the first 16 weeks of treatment.

8.4 Pediatric Use

The safety and efficacy of DUPIXENT have been established in pediatric adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis. The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

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

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 308 subjects 6 to 11 years of age with severe atopic dermatitis (Trial 3). The safety profile of DUPIXENT + TCS in subjects through Week 16 was similar to the safety profile from trials in adults and adolescents with atopic dermatitis. The long-term safety of DUPIXENT + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (Trial 7). Among subjects who entered this study, 19% had moderate and 72 (20%) had severe atopic dermatitis at the time of enrollment in Trial 7. The safety profile of DUPIXENT + TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in Trial 8. The long-term safety profile of DUPIXENT + TCS observed in pediatric subjects was consistent with that seen in adults and adolescents with atopic dermatitis [see Pediatric Use (8.4)].

Specific Adverse Reactions

Conjunctivitis and Keratitis

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

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 52-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).
Hypersensitivity Reactions
Hypersensitivity reactions were reported in <1% of DUXPENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis [see Clinical Pharmacology (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)].

Eosinophilia
DUXPENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophil counts from baseline to Week 4 were 100 and 0 cells/ml, respectively. Across all indications, the incidence of treatment-emergent eosinophilia (>500 cells/ml) was similar in DUXPENT and placebo groups.

Treatment-emergent eosinophilia (≥5000 cells/ml) was reported in <2% of DUXPENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

Cardiovascular (CV)
In the 1-year placebo-controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatalfatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUXPENT 200 mg Q2W group, 2 (1.8%) of the DUXPENT 300 mg Q4W group, and 0 (0.0%) of the placebo group.

5.2.1 Moderate-to-Severe Atopic Dermatitis

5.2.2 Moderate-to-Severe Eosinophilic Dermatitis

5.2.3 Moderate-to-Severe Nummular Dermatitis

5.2.4 Moderate-to-Severe Chronic Idiopathic Urticaria

5.2.5 Moderate-to-Severe Bacterial Skin
defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUXPENT and any potential adverse effects on the breastfed child from DUXPENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis
The safety and efficacy of DUXPENT have been established in pediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis. Use of DUXPENT in this age group is supported by Trial 6 which included 251 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis. Use of DUXPENT in this age group is supported by Trial 6 which included 251 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis. Use of DUXPENT in this age group is supported by Trial 6 which included 251 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis.

8.5 Geriatric Use

The safety and efficacy of DUXPENT in patients aged 65 years and older have not been established. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUXPENT during pregnancy. Encourage participation in the registry [see Use in Specific Populations (8.1)].

Administration Instructions
Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the handling, timing of sample collection, concomitant medications, and the observed incidence of antibodies 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 DUXPENT 300 mg Q2W for 52 weeks developed antibodies (ADA) against 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 DUXPENT 200 mg Q2W or 300 mg Q4W for 16 weeks. Approximately 16% of adolescent subjects with atopic dermatitis who received DUXPENT 200 mg Q4W for 16 weeks developed antibodies to dupilumab; ~3% exhibited persistent ADA responses, and ~5% had neutralizing antibodies.

Regard less of disease population, ~2 to 4% of subjects in the placebo group were positive for antibodies to DUXPENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies. The antibody detected in both DUXPENT and placebo subjects were mostly low. In subjects who received DUXPENT, 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 DUXPENT therapy [see Warnings and Precautions (5.1)].

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

Skin and subcutaneous tissue disorders: Facial Rash

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUXPENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which adult subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUXPENT administration, subjects were vaccinated with an inactivated Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUXPENT during pregnancy. Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dxent/ to enroll in or to obtain information about the registry.

Risk Summary
Available data from case reports and case series with DUXPENT use in pregnancy were not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to be cross the placental barrier; therefore, DUXPENT may be transferred to the developing fetus. In the observed pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to ~10-times the maximum recommended human dose (MRHD) [see Data]. The estimated background risk of major birth defects and miscarriage for the unvaccinated populations is unknown. All pregnancies are inherently at risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data
In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous 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 embryonic toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary
There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production.

Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUXPENT and any potential adverse effects on the breastfed child from DUXPENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis
The safety and efficacy of DUXPENT have been established in pediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis. Use of DUXPENT in this age group is supported by Trial 6 which included 251 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis and Trial 8 which included 367 children 6 to 11 years of age with severe atopic dermatitis. The safety and efficacy were generally consistent between pediatric and adult patients [see Adverse Reactions (6.1) and Clinical Studies (14.1) in the full prescribing information].

Use is also supported by Trial 7, an open-label extension study that enrolled subjects who completed Trials 6 and 8. Trial 7 included 136 adolescents from Trial 6 and 110 children from Trial 8. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis at enrollment into the extension study. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis. No new safety signals were identified in Trial 7 [see Adverse Reactions (6.1)].

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

8.5 Geriatric Use

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

10 OVERDOSE

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

17 PATIENT COUNSELING INFORMATION

Advises 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 DUXPENT during pregnancy. Encourage participation in the registry [see Use in Specific Populations (8.1)].

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the handling, timing of sample collection, concomitant medications, and the observed incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Additionally, the observed incidence of antibodies 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 DUXPENT 300 mg Q2W for 52 weeks developed antibodies (ADA) against dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Regard less of disease population, ~2 to 4% of subjects in the placebo group were positive for antibodies to DUXPENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies. The antibody detected in both DUXPENT and placebo subjects were mostly low. In subjects who received DUXPENT, 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 DUXPENT therapy [see Warnings and Precautions (5.1)].

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

Skin and subcutaneous tissue disorders: Facial Rash
The research landscape for atopic dermatitis looks promising with several therapies in late-stage development. But safety issues have clouded the future of one important class of drugs, and drug developers are hopeful that their products will be on the market soon.

And the market that they are eyeing is huge. Atopic dermatitis affects about 7% of adults in the United States. Of those affected, about 40% have moderate or severe symptoms that may need more advanced and expensive treatment.

Atopic dermatitis is a chronic inflammatory skin disorder that can cause intense, persistent itching. It is called atopic dermatitis because atopy is a genetic predisposition to develop allergies and dermatitis is inflammation of the skin. When skin is healthy, it tends to retain moisture and fend off bacteria and allergens. In people with atopic dermatitis, the skin is less protective and therefore vulnerable to irritants and allergens. Sometimes atopic dermatitis is called atopic eczema, and atopic dermatitis and eczema are often used interchangeably, although strictly speaking, atopic dermatitis is one of many forms of eczema.

Topical treatments — emollients and moisturizers — help many patients. Phototherapy, which can reduce histamine production, is an option. But some patients don’t respond to these and other treatments.

“We’ve had very few new options available to offer patients. Now we have several new therapies pending approval in the United States that could transform the therapeutic landscape for a topic dermatit,” says Jonathan Silverberg, M.D., Ph.D., associate professor of dermatology at George Washington University School of Medicine and Health Sciences.

The only systemic biologic therapy on the market for the disease is Dupixent (dupilumab), a monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13), cytokines that play a role in inflammation and the immune response. Developed by Regeneron and Sanofi, Dupixent is approved for three indications: moderate to severe atopic dermatitis in people 6 years and older, as an add-on maintenance therapy for moderate to severe asthma in people 12 years and older, and as an add-on therapy in adult patients with chronic rhinosinusitis with nasal polyps.

Other monoclonal antibodies that inhibit IL-13 are in development. Results of phase 3 clinical trial of Eli Lilly’s lebrikizumab showed that it improves skin clearance and itch. In August 2021, Lilly released interim results of two trials that are evaluating lebrikizumab as a monotherapy in adult and adolescent patients with moderate to severe atopic dermatitis. Lebrikizumab also achieved key secondary end points versus placebo in patients with atopic dermatitis, including early onset in skin clearance and itch relief, improvement in interference of itch on sleep and quality of life. “The top-line results line results look quite impressive in terms of improvements of both skin clearance and improvements of quality of life, including itching and other...
“Now we have several new therapies pending approval in the United States that could transform the therapeutic landscape for atopic dermatitis.”

— JONATHAN SILVERBERG, M.D., PH.D., ASSOCIATE PROFESSOR OF DERMATOLOGY AT GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND HEALTH SCIENCES

symptoms,” says Silverberg, who is also a principal investigator for one of the lebrikizumab trials. The full results from the two lebrikizumab trials will be released in 2022, officials from Lilly said. Data from a different phase 3 trial of the combination lebrikizumab with topical corticosteroids in patients with atopic dermatitis will by the end of 2021.

Another monoclonal antibody that targets IL-13 is Leo Pharma’s Adtralza (tralokinumab), which received approval in Europe in June 2021 for the treatment of adult patients with moderate to severe atopic dermatitis. This approval was based on three phase 3 trials that included 1,900 patients and demonstrated significant improvements in signs and symptoms, with treatment response rates gradually improved and maintained over time. But FDA issued a complete response letter — essentially a nonapproval — for Adtralza in April 2021 and requested additional data related to the device component of the therapy. “The response letter was not related to the drug itself,” Silverberg says. “The FDA requested technical information about the syringe that is used. This seems like a unique situation that probably is not relevant or generalizable to the class.”

**Five JAK inhibitors**
The pipeline of atopic dermatitis treatment also includes several drugs in the Janus kinases inhibitor class. Janus kinases (JAK) are signaling enzymes within cells that activate interleukin receptors, so inhibiting them has the effect of reducing interleukin activity and therefore inflammation. JAK inhibitors are seen a promising class of medication partly because inflammation is the root cause of so many conditions, and JAK inhibition is broadly anti-inflammatory.

The FDA has approved a total of five JAK inhibitors: three for inflammatory conditions and two for blood disorders. The three approved for inflammatory conditions are Pfizer’s Xeljanz (tofacitinib), Eli Lilly’s Olumiant (baricitinib) and AbbVie’s Rinvoq (upadacitinib). Xeljanz has been approved for rheumatoid arthritis and several other conditions; Olumiant and Rinvoq, for rheumatoid arthritis. The agency has also issued an emergency use authorization for Olumiant as treatment for hospitalized patients with COVID-19 and approved Opzelura (ruxolitinib), a topical formation of a JAK inhibitor, as a treatment for atopic dermatitis. Incyte’s Jakafi (ruxolitinib) is approved to graft-versus-host disease in patients 12 years and older, as well as a type of blood cancer called polycythemia vera in adults. Celgene’s Inrebic
(fedratinib) is approved as a treatment for myelofibrosis, a bone marrow disorder.

In January 2021, the JAK inhibitors hit a major bump in the road. A postmarketing cardiovascular safety trial of Xeljanz in patients with rheumatoid arthritis found there was a higher risk of cardiovascular adverse events in patients treated with Xeljanz. Pfizer’s study compared Xeljanz with a TNF inhibitor and included 4,362 patients. The primary analyses included 135 patients with major adverse cardiovascular events (MACE) and 164 subjects with malignancies (excluding nonmelanoma skin cancer). The most frequently reported MACE was myocardial infarction, and the most frequently reported malignancy was lung cancer. In those patients with a higher prevalence of known risk factors and malignancy — such as older age and smoking — a higher occurrence of events was seen across all treatment groups.

As a result, in September, the FDA started requiring the JAK inhibitors to carry a warning about the increased risk of serious heart-related events such as heart attack, stroke, cancer, blood clots and death. But the warning only applies to medications used to treat arthritis and inflammatory conditions. Jakafi and Inrebic are not subject to the warnings, agency officials said, because they are used to treat blood disorders and they require different updates.

**Missed PDUFA dates**

The findings have resulted in FDA officials looking more closely at safety issues of Xeljanz and other therapies in the JAK inhibitor class. Several JAK inhibitors with applications under review have missed their Prescription Drug User Fee Act (PDUFA) dates — a date by which the agency is supposed to make a decision on a drug’s application for approval — as the regulatory agency takes more time to review the class.

“From an efficacy standpoint, the JAK inhibitors look very promising and even appear to be more effective than Dupixent in head-to-head studies and in a meta-analysis, at least for some end points in certain time points,” says Silverberg said. “But the FDA has given an indication of clear concerns around safety. We’re waiting to hear back about what the agency will do with respect to their approval in atopic dermatitis.”

Earlier this year, several companies announced the agency would miss the PDUFA dates for their JAK inhibitors that were under review as treatments for atopic dermatitis and other indications. Pfizer’s abrocitinib is one of the JAK inhibitors in a holding pattern. Results of a Pfizer-supported phase 3 trial of two different doses of abrocitinib reported in the March 25, 2021, issue of the *New England Journal of Medicine* showed that both improved symptoms.

The FDA is also reviewing AbbVie’s application for Rinvoq as a treatment for atopic dermatitis. European regulators approved Rinvoq for atopic dermatitis in August 2021. AbbVie announced in July that the application for treatment of atopic dermatitis would miss its PDUFA date. The company had previously announced that the application for Rinvoq as treatment for psoriatic arthritis and ankylosing spondylitis would also miss its PDUFA date.

News of the delays came as results of a favorable, AbbVie-supported head-to-head study were reported in the August 2021 issue of *JAMA Dermatology*. Of those treated with Rinvoq, 71% achieved Eczema Severity Index, a commonly used measure of treatment effect in atopic dermatitis, at week 16 compared with 61% of those treated with Dupixent. Additionally, Rinvoq demonstrated statistically significant greater efficacy across all ranked secondary endpoints compared to Dupixent through week 16, including early reduction in itch and rates of skin clearance improvement. The most common adverse events were acne for the Rinvoq group and conjunctivitis for the Dupixent group.

Olumiant also missed its PDUFA date. It is approved in more than 40 countries as a treatment for moderate-to-severe atopic dermatitis in adults.

Further back in the pipeline for atopic dermatitis is nemolizumab, a monoclonal antibody directed against IL-31 being developed by Galderma. IL-31 plays a role in directly stimulating sensory neurons related to itch and contributes to inflammation. Results from a phase 2 study show nemolizumab-treated patients experienced significant itch relief within 48 hours of treatment, which was sustained at week 16.
Ten months into the Biden administration and no one has been nominated to be the permanent FDA commissioner, let alone confirmed. The void reflects the high stakes involved in the position and the bramble of political tensions that have engulfed the federal regulatory agency. But those are some of the very same reasons the agency needs someone at the helm, say many observers and people in the industries that the FDA regulates. “All nominations to healthcare agencies are essential during the global public health crisis. They’re essential all the time, but even more so during this period,” says Alec Stone, public affairs director of the Oncology Nursing Society.

Mid-October, an apparent front-runner for the nomination seemed to emerge. Numerous news outlets reported that President Biden was getting ready to nominate Robert Califf, M.D., MACC. Califf would appear to be a relatively safe choice; he was one of the FDA commissioners during the Obama administration. But as we went to press, there was still no official announcement, so uncertainty about who would be running the FDA lingered.

Janet Woodcock, M.D., has been the acting commissioner since Biden’s inauguration at the beginning of this year. Woodcock, who has worked at the agency for 35 years, was once considered among the finalists for nomination to be the permanent commissioner. Her backers credited her with speeding up the FDA’s drug approval process and getting more therapies approved, particularly cancer treatments. Her detractors flipped the script and accused her of lowering FDA standards and allowing questionable drugs on the market. Sen. Joe Manchin, among others, cast blame for the opioid epidemic on Woodcock. “The FDA has played a critical role in this overdose epidemic by overseeing continuous approvals of stronger and more addictive opioids since the initial approval of OxyContin in 1995 — and Dr. Woodcock has been there for all of it,” Manchin wrote in an open letter in June. The agency’s controversial approval of Aduhelm (aducanumab) for treatment of Alzheimer’s disease also possibly worked against Woodcock. Numerous media outlets reported in mid-August that the White House had decided against nominating her. “There have been little hiccups along the way, and everything is political,” Stone says. “I don’t think anyone is suggesting she’s not qualified and experienced.”

Technically, Woodcock was allowed to serve as acting commissioner for a period of just 210 days, which ended in mid-August. But the Federal Vacancies Reform Act of 1998 allows an additional 90 days of service if the vacancy existed at inauguration or became vacant in the 60 days following inauguration. That 90-day period ends Nov. 15. The clock restarts, though, if and when the Biden administration nominates a candidate for the permanent job, which would give Woodcock another 210 days until that nominee is confirmed, withdrawn, returned or rejected.

Politics as unusual
There are exceptions, such as Scott Gottlieb, M.D., and David Kessler, M.D., but throughout much of the FDA’s 115-year history, most of its commissioners have kept a relatively low profile. The pandemic changed that. Questions about whether the agency caved to pressure from the Trump administration clouded Stephen Hahn’s tenure as commissioner. The agency approved and then revoked an emergency use authorization for hydroxychloroquine, the antimalarial drug that former President Donald Trump promoted as treatment for COVID-19.

Why doesn’t the FDA have a permanent commissioner?

The agency has been in the spotlight because of the pandemic, questions about its independence and the approval of Aduhelm. The stakes are high and the politics, fraught. by DEBORAH ABRAMS KAPLAN
for COVID-19. Hahn also ended up apologizing for mischaracterizing the effectiveness of convalescent plasmas as treatment for the disease.

“It’s been an unusual Washington parlor game,” Stone says of the people who argued for or against Woodcock. Califf would be a “very solid choice,” in Stone’s view. He is familiar with the agency and having served in the Obama Administration means that he and Biden likely have a good working relationship, Stone says.

Too friendly?
The FDA is probably best known for regulating drugs and vaccines, but it also has regulatory oversight of much of the food, cosmetics, medical device and tobacco products industries. By the agency’s own reckoning, FDA-regulated products account for about one-fifth of annual spending by U.S. consumers, which works out to be roughly $2.8 trillion.

How the agency wields its powers has changed over the years. Decades ago, the FDA was more of a policing organization to protect the public from potentially harmful drugs, says Sharon Ayd, Ph.D., MBA, an industry consultant. In the 1960s, Frances Oldham Kelsey, an FDA reviewer, was responsible for keeping thalidomide, a morning sickness drug that caused birth defects, off the market in the U.S.

But the agency started to work more closely with the pharmaceutical industry in the early 1990s partly because of the 1992 Prescription Drug User Fee Act, which, among other changes, set up a system of industry fees to support the agency’s drug approval process in exchange for speeding up that process and setting deadlines.

Ayd credits Gottlieb, who was commissioner from 2017 to 2019, with bringing more change to the agency by fostering a constructive working relationship with drug developers. FDA officials now start talking and working with drug discovery companies earlier. The culture of remaining open to new ideas and science continues, she says, “and that’s a great thing.” The FDA now allows practices that it once frowned upon if not prohibited, such as allowing some compounds to go into patients earlier for dose-escalation studies and companies to use surrogate markers to prove effectiveness. And with adaptive clinical trial design, trials can happen in parallel with FDA data review. “That’s why Operation Warp Speed was possible,” Ayd says. Otherwise, developing a vaccine can take up to 30 years and still not be effective. “But the reason it worked was because the red tape got taken away, and the government, from the president’s office and probably from the head of the FDA, said ‘Don’t worry about making a mistake.’ But other than a pandemic, we always worry about making mistakes.”

But the approval of Biogen’s Aduhelm is seen by many as evidence that the agency has become too accommodating of drug developers and permissive in its approvals. Aaron Kesselheim, M.D., J.D., M.P.H., a professor at Harvard Medical School and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women’s Hospital in Boston, called the Aduhelm approval “probably the worst drug approval decision in recent U.S. history” in his resignation letter from the advisory committee that had recommended against approval. Stat reported on a history of unusual contact between FDA and Biogen officials when Aduhelm was foundering. After the approval, Woodcock requested an investigation from the U.S. Department of

### FDA-Registered Facilities

<table>
<thead>
<tr>
<th>Program</th>
<th>Domestic</th>
<th>Foreign</th>
<th>Total</th>
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<tbody>
<tr>
<td>Animal Drugs</td>
<td>1,608</td>
<td>1,156</td>
<td>2,764</td>
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<tr>
<td>Animal Food</td>
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<td>25,023</td>
<td>65,849</td>
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<td>Biologics</td>
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<td>467</td>
<td>5,579</td>
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<td>Human Drugs</td>
<td>3,568</td>
<td>3,970</td>
<td>7,538</td>
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<tr>
<td>Human Food</td>
<td>90,646</td>
<td>131,844</td>
<td>222,490</td>
</tr>
<tr>
<td>Medical Devices</td>
<td>13,010</td>
<td>12,854</td>
<td>25,864</td>
</tr>
<tr>
<td>Tobacco</td>
<td>3,067</td>
<td>0</td>
<td>3,067</td>
</tr>
</tbody>
</table>

Source: U.S. Food & Drug Administration
Why doesn’t the FDA have a permanent commissioner? | Industry Analysis

THERE’S A LOT ON THE PLATE

The FDA’s responsibilities go far beyond just approving drugs. The industries that the FDA regulates touch every American’s life. Here is a brief list of what is in the agency’s portfolio:

- Oversight of more than $2.8 trillion in consumption of food, medical products and tobacco
- Regulation of 78% of the U.S. food supply (it doesn’t regulate meat, poultry and some egg products)
- Has approved more than 20,000 prescription drugs
- Oversight of 6,500 medical device products
- Oversight of 90,000 tobacco products
- Has licensed about 300 biologics
- Has approved 1,600 animal drug products

Source: FDA, “FDA at a Glance,” November 2020

Health & Human Services’ Office of Inspector General, citing concerns about those contacts.

Some precedent
But the FDA and its commissioners are not exactly strangers to politics and controversy. Kessler, for example, was pilloried for promoting a “nanny state” because of steps he took to regulate the food and tobacco industries and by AIDS activists for not pushing the agency to approve drugs faster. Ned Sharpless, M.D., director of the National Cancer Institute, served as acting commissioner for six months and was touted as a successor to Gottlieb instead of Hahn, but it was widely reported that the Trump White House crossed him off the list partly because he had contributed to the campaigns of Democrats. Gottlieb faced criticism for taking a tough stance on vaping.

Nor is the lack of permanent leadership without precedent. During the George W. Bush administration, the agency was headed by a series of interim commissioners for the better part of two years. “A continuous ‘interim director’ at FDA is like a babysitter left in charge of the children indefinitely — you don’t want to leave important decisions to that person,” said an influential congressman at the time.

“The FDA and professionals who work there have their goals and missions in their respective centers, promoting safety and efficacy,” says Stone. That said, a permanent commissioner would help solidify the agency’s priorities and long-term agenda. Those outside the agency are worried about the long-term agenda. “This is a major appointment in the healthcare environment, and many provider and advocacy groups are looking forward to a permanent commissioner. It’s not about tomorrow. It’s about next year,” Stone says.

Obviously, Biden officials want a nominee with enough votes in the Senate to win confirmation, so Manchin and a handful of other senators have more leverage. “In a 50-50 Senate, finding a nominee who will garner bipartisan support is the goal, even required,” notes Stone. Califf might fit the bill. He was a low-key FDA commissioner during the Obama administration and was in the job for just 11 months.

“The FDA commissioner’s job is to walk that fine line between following the evidence and staying independent while being attuned to time constraints, stakeholder concerns and, yes, politics and public attitudes. With social media and a 24-hour news cycle, “it’s easy to pick up on anything and sensationalize it,” Stone says. “There are more hurdles today, more eyes watching. There’s a balance between what they need to do and what they’re being pushed to do from the outside, whether approving drugs faster or slowing down the process because we’re not sure what the evidence is.” Plus, the pandemic has brought to the surface beliefs and attitudes that dismiss science and conventional medicine. As an agency that depends on science and evidence, the FDA and its commissioner may need to combat those formerly fringe ideas.

“There’s a bit of a disconnect with the American public in understanding the roles of agencies with oversight,” says Stone.

Deborah Abrams Kaplan writes about medical and practice management topics.
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

For patients with Homozygous FH (HoFH) aged 12 years or older

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

The LDL-C-lowering effect of EVKEEZA may be measured as early as 2 weeks. At week 24, the LS mean treatment difference between EVKEEZA and placebo in mean percent change in LDL-C from baseline was -49% (95% CI: -65% to -33%; P<0.0001). LS mean percent change in LDL-C from baseline with EVKEEZA was -47% and with placebo was +2%.

**INDICATION**

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

**Limitations of Use:**

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

**IMPORTANT SAFETY INFORMATION**

**Contraindication**

EVKEEZA is contraindicated in patients with a history of serious hypersensitivity reactions to evinacumab-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** to learn more about EVKEEZA
EVKEEZA® lowered LDL-C by ~50%, on average, at 24 weeks¹

**Study design**

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

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

A key secondary endpoint was the LS mean change in LDL-C from baseline to week 24. At week 24, the LS mean change in LDL-C from baseline for patients receiving EVKEEZA was -135 mg/dL compared with -3 mg/dL for patients receiving placebo (treatment difference -132 mg/dL; 95% CI: -175 to -89; P < 0.001).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.²

Importantly, EVKEEZA lowered LDL-C by an average of 135 mg/dL from baseline in patients receiving EVKEEZA²

**IMPORTANT SAFETY INFORMATION (continued)**

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

**Adverse Reactions**

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

**Use in Specific Populations**

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

**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 development 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.

EVKEEZA (evinacumab-dgnb) injection, for intravenous use

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 heterozygous familial hypercholesterolemia (HeFH).
- 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. Serious hypersensitivity reactions, including anaphylaxis, have occurred [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Serious Hypersensitivity Reactions
Serious hypersensitivity reactions have occurred with 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 rabbits. Administration of evinacumab to rabbits during organogenesis caused increases in fetal malformations at doses below the human exposure. Advise pregnant patients who may become pregnant of the potential risk to the 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 in adult and pediatric patients of Evinacumab (EVKEEZA). The most common adverse reactions (reported in greater than 3% of EVKEEZA-treated patients and greater than placebo) are shown in Table 1.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=60)</th>
<th>EVKEEZA (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Flushing</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Asthma</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

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 0% patients who received placebo. The following infusion reactions occurred in EVKEEZA-treated patients: infusion site pruritus, pyrexia, muscular weakness, nausea, and nasal congestion.

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) post-therapy 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 EVKEEZA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

No patients developed treatment-emergent antibodies to EVKEEZA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
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 be present in human milk. When administered to pregnant patients, EVKEEZA has the potential to be transmitted from the mother to the developing fetus.

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

If a patient becomes pregnant while receiving EVKEEZA, healthcare providers should report EVKEEZA exposure by calling 1-833-385-3392.

Data
Animal Studies
In an embryo-fetal development study in pregnant rabbits,evinacumab-dgnb was administered subcutaneously at doses of 5, 10, 30 and 100 mg/kg every 3 days (Q3D) during the period of organogenesis from gestation day 7 to day 19. Evinacumab-dgnb was teratogenic in rabbits, causing domed head, dilation of the lateral and third ventricles of the brain, and flexed fore/hind paws at maternal evinacumab-dgnb exposures below human exposure at the MRHD of 15 mg/kg every 4 weeks, based on AUC. Other fetal malformations, consisting of irregular and abnormal ossification, split skull, dilated lateral ventricles, and metacarpal, and enlarged anterior and/or posterior fontanelles observed and were consistent with significant maternal toxicity (including early deaths due to abortion and premature delivery at all doses) reduction in maternal body weight gains, and reduced maternal food consumption. Increased incidences of post-implantation losses, resorptions (total, early, and late), and decreased fetal body weight were also consistent with maternal toxicity. Evinacumab-dgnb was present in the sera of fetuses born from mothers at 10 and 30 mg/kg/Q3D at levels higher than in maternal serum.

In an embryo-fetal development study in pregnant rats,evinacumab-dgnb was administered subcutaneously at doses of 5, 10, 30 and 100 mg/kg/Q3D during the period of organogenesis from gestation day 6 to day 18. Maternal exposures to evinacumab-dgnb were below the human exposure measured at the MRHD of 15 mg/kg every 4 weeks, based on AUC. Other fetal malformations, consisting of irregular and abnormal ossification, split skull, dilated lateral ventricles, and reduced maternal food consumption. Increased incidences of post-implantation losses, resorptions (total, early, and late), and decreased fetal body weight were also consistent with maternal toxicity. Evinacumab-dgnb was present in the sera of fetuses born from mothers at 10 and 30 mg/kg/Q3D at levels higher than in maternal serum.

12 years and older. Use of EVKEEZA for this indication is supported by evidence from adequate and well-controlled trials in adults with additional efficacy and safety data in pediatric patients aged 12 years and older. Use of EVKEEZA for this indication is supported by evidence from adequate and well-controlled trials in adults with additional efficacy and safety data in pediatric patients aged 12 years and older [see Adverse Reactions (6.1) and Clinical Studies (14)]. The safety and effectiveness of EVKEEZA have not been established in pediatric patients with HoFH who are younger than 12 years old.

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)].

8.4 Pediatric Use
The safety and effectiveness of EVKEEZA as an adjunct to other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 12 years and older. Use of EVKEEZA for this indication is supported by evidence from adequate and well-controlled trials in adults with additional efficacy and safety data in pediatric patients aged 12 years and older [see Adverse Reactions (6.1) and Clinical Studies (14)]. The safety and effectiveness of EVKEEZA have not been established in pediatric patients with HoFH who are younger than 12 years old.

8.5 Geriatric Use
Clinical studies of EVKEEZA did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently from younger adult patients.

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Obesity and diabetes disproportionately affect Latinos in the United States, a group that comprises 18.4% of the population, or approximately 60.5 million people. Latinos are 1.2 times more likely to be obese than non-Latino Whites, according to the HHS Office of Minority Health. Almost 4 out of 5 (78.8%) Hispanic women are overweight or obese compared with 64% of non-Latino White women. Latinos are twice as likely to have type 2 diabetes (17%) than Whites (8%), according to the CDC. The average adult in the United States has a 40% chance of developing type 2 diabetes, but Latino adults have a greater than 50% chance. Furthermore, Latinos are more likely to develop diabetes at a younger age than the average American and therefore are exposed to its negative effects longer.

Although the interplay genetics and environment certainly plays some causative role, social determinants of health are a leading — and modifiable — factor in the complicated, web of factors and influences that affect the health of Latinos in the U.S.

Consider these statistics from a 2019 report by the HHS Office of Minority Health:

- Latinos have the highest uninsured rates of any racial or ethnic group within the United States; 50.1% of Latinos had private insurance coverage compared with 74.7% of non-Latino Whites.
- Among full-time, year-round workers, the average Hispanic median household income was $55,658 compared with $71,644 for non-Latino White households.
- The unemployment rate for Latinos was 5.1% compared with 3.7% for non-Latino Whites.

Factors that lead to obesity

“Obesity results from an imbalance of calorie consumption and inadequate physical activity, which is persistent among Latinos,” says Anabell Castro Thompson, M.S.N., APRN, ANPC, FAAN, FAANP, senior vice president of health equity at Equality Health in Phoenix. “Furthermore, as with many other health issues affecting the Latino community, this problem is exacerbated by the inaccessibility and unaffordability of healthcare.”

People who lack adequate health insurance often don’t have a primary care provider, so they are less likely to get continuity of care and help with prescription adherence, Castro Thompson says. They also are less likely to seek preventive services and may instead obtain care in expensive emergency room settings.

Franz Monroy, M.D., M.P.H., M.S., associate medical director of family medicine at Intermountain Healthcare in Salt Lake City, believes the high cost of healthy foods and easy access to less expensive, high-calorie fast food options contribute to less-than-ideal food choices for some Latinos.

“When finances are tight and time is short, it takes less time and money to purchase fast food from a restaurant than it (does) to buy fruits and vegetables and prepare meals at home,” he says. Additionally, many cultural factors contribute to obesity. For example, some Latino families — especially those who have experienced food insecurities in the past — may see being overweight as an indicator of being in good health and having a higher socioeconomic standing. “Some Latino families think that a fat baby is a healthy baby,” Monroy says. “Children are often encouraged to eat their entire meal even if they’re full, a practice that can lead to overeating as an adult.”

Reducing obesity rates

To reduce incidence rates and costs associated with obesity among Latinos, providers need to adopt a team-based holistic care approach...
that accounts for medical, behavioral and cultural factors, as well as social and economic needs.

“Some Latinos live in areas of high poverty and food deserts and lack access to adequate or stable housing, transportation and good-paying jobs,” Castro Thompson says. “Providers need to be aware of these potential challenges and screen patients for information related to their social determinants of health. Then they should connect patients to community resources that can address any issues they have. Strong connections between providers and community-based organizations are essential because patients spend most of their time in their communities rather than engaging directly with the healthcare system.”

Based on his experience with his patients, Monroy says Latinos’ lower incomes and decreased access to healthcare contribute to their higher rates of diabetes. A lack of access to healthcare makes it less likely that patients will be seen for preventive visits. That can mean they may not be screened for diabetes and other conditions that are potentially preventable — or at least more easily managed at earlier stage.

“Very few Latino patients make a point to have a preventive visit,” Monroy says. “For some, it’s understandable that they don’t want to leave work if they don’t have a specific concern, which could potentially mean a loss of income and subsequent economic burden. Others don’t want to miss work for fear of losing their jobs. But by not getting seen, I can’t screen people for diabetes, discuss what (makes up) a healthy diet, or review the importance of exercise and weight loss, all of which aid in diabetes prevention.”

As with obesity, diet and lifestyle also are major contributors higher diabetes rates in Latinos. Some traditional Latino foods and ingredients, such as flour tortillas, refried beans, lard, fatty cuts of meat, cheese and cream, are high in fats and calories. There can be cultural pressures to overeat, specifically in the setting of family gatherings and celebrations. “There is typically a negative association (with) declining food, which is often seen as being rude or not culturally acceptable. Generally, (fewer) leisure time activities are exercise focused,” Monroy notes.

How to lower rates

Castro Thompson believes that reducing incidence rates and costs associated with diabetes in the Latino community requires improvements in affordability, accessibility and equity. “Accessibility needs to be expanded beyond medical care and should include prompt access to behavioral health needs and making connections to socioeconomic needs,” she says.

Patient education, whether written or spoken, should be in the correct language and at the right literacy level, which is critical to helping Latino patients better manage diabetes, Castro Thompson says. Providers should also assess patients for social determinants of health and connect them to community resources that can assist with access to healthy foods, housing insecurity, and even with paying for utilities, which is important because insulin, used to manage diabetes, requires refrigeration.

Finally, it’s important to build providers’ cultural competence so they can understand how cultural preferences and beliefs play a role in diabetes medication adherence and preventive care. Patients with diabetes need healthcare services to help them avoid complications such as diabetic retinopathy, neuropathy and amputations, Castro Thompson says. □

**Karen Appold** is a medical writer in the Lehigh Valley region of Pennsylvania.
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When her toddler was diagnosed with progeria in 1998, Leslie Gordon, M.D., Ph.D., faced three distinct challenges: Progeria was extremely rare. It was incurable. And most devastatingly, it was fatal.

Gordon’s son, Sam Berns, had appeared healthy at birth, but by the time he turned 2, it was clear that something was wrong. Caused by a mutation in the LMNA gene, progeria leads to rapid aging and physical changes, culminating in an early death. Not only was there no cure for progeria, but there was no treatment, no pipeline and no awareness. Nothing. “The story with rare diseases is a well-trodden one, and there was nothing out there for us,” she says.

Gordon, though, decided to fight. Her husband, her sister and she pooled their talents and set about ticking off a daunting to-do list: find children with progeria, create an international registry, launch a cell and tissue bank and raise money. The result was the Progeria Research Foundation. Sam died in 2014, but the foundation’s work continues. The FDA approved the first-ever therapy for patients with progeria, Zokinvy (lonafarnib), last year. Gordon says the approval is a breakthrough not only from a medical standpoint but also from a societal one. "It’s a reminder that we can make a difference," she says.

The Pfizer and Moderna COVID-19 vaccines introduced much of the world to ribonucleic acid (RNA), which has long played second fiddle to DNA. But in addition to the messenger RNA vaccines, treatments targeting and using RNA in a variety of ways are filling the pipeline and exciting researchers and drug developers.
psychological one. "It just puts us in a whole different place," she says, "a whole different mindset."

Yet an even more dramatic leap forward could be on the horizon. Two different research teams are working on a new strategy to fight progeria based on the idea that ribonucleic acid (RNA) can be leveraged or inhibited in ways to prevent or cure a host of diseases. The investigational therapies are part of a wave of new RNA agents that could one day reshape large portions of the therapeutic landscape.

Tom Misteli, Ph.D., who directs the Center for Cancer Research at the National Cancer Institute, is working on one such investigational therapy, known as LB143. He notes that the DNA mutation underlying progeria causes defective processing of critical cellular RNA, leading to the creation of a mutant protein called progerin. By inhibiting production of the RNA coding for the defective protein, investigators hope to slow down the disease. In research findings published this past March, Misteli and colleagues showed that the strategy reduced progerin-producing RNA by 90% to 95%.

Development of another RNA-based product, led by current National Institutes of Health Director Francis S. Collins, M.D., Ph.D., is also showing early promise. In a mouse model of progeria, the agent increased survival by 60%.

**RNA ADVANTAGES**

RNA has long lived in the shadow of DNA, famous for its sinuous double helix shape and analogized to being the genetic blueprint of all life. RNA has a less elegant single strand and is frequently depicted as being the dutiful reader of DNA, the plodding translator of its complex instructions.

But some might say that RNA is having its day. The Pfizer and Moderna COVID-19 vaccines are messenger RNA vaccines, crafted to carry instructions for the making the telltale spike protein of the SARS-CoV-2 virus that trains the immune system to recognize and attack when it next encounters a SARS-CoV-2 infection. Traditional vaccines depended on growing pathogens in cell culture. Most flu shots are still contingent on growing influenza viruses in eggs. The stunning speed at which the Pfizer and Moderna vaccines were developed has been attributed to their dependence on RNA, which with today’s technologies is relatively easy to modify and keep stable.

Treatments involving RNA are taking off and filling the drug development pipeline. Some are scraps of DNA designed to keep messenger RNA from making proteins. Others operate on RNA processes so mutated portions don’t get expressed and eventually made into aberrant, disease-causing protein.

"Superficially, it’s a no-brainer. The DNA makes the RNA. The RNA makes the proteins," Gordon says. If the proteins are the problem, disrupting that process could lead to a resolution — in theory. "Then, when you get into it, science is always more complicated," she says.

Phillip D. Zamore, Ph.D., a pioneer in RNA therapies and chair of the RNA Therapeutics Institute at the University of Massachusetts, said RNA therapies represent a novel way of thinking about stopping diseases. Traditionally, small-molecule drugs target the enzymatic activity of proteins. "All of those are old-fashioned drugs, in the sense that they require searching through huge libraries of compounds to fortuitously find a lead compound that your medicinal chemists could turn into a drug," he says.

Next-generation RNA therapies create a new opportunity to disrupt the transfer of information within cells, thereby interfering with the process underlying the target disease. Misteli says RNA makes the best target within the DNA-to-RNA protein relay. He notes that genetic information is permanently encoded in DNA, but changing the underlying genetic code carries risk and could lead to unintended consequences. Another option is interfering with proteins, but that solution is not particularly efficient, he says. RNA, on the other hand, provides a meaningful target without the risks of DNA alteration. "Targeting RNA offers the benefit of eliminating the effect of a mutation close to the source yet without a permanent change to the hereditary information," he says.

Zamore identifies two key turning points that helped transform RNA-targeting therapies from an idea into a reality. The first was the discovery that antisense oligonucleotides (also called antisense oligos) could interfere with RNA splicing, an intermediate step in the formation of messenger RNA. That led to the development of the first RNA therapy, Vitravene (fomiviren), which the FDA approved in 1998 as a treatment for patients with cytomegalovirus retinitis, a vision-threatening disease most commonly known as a complication of HIV/AIDS at the time. However, antisense oligos never worked all that well in suppressing messenger RNA expression, Zamore says, limiting their usefulness. Instead, one more step was necessary, the discovery that double-stranded
The RNA moment

small interfering RNA (siRNA) could be used to interfere with RNA or RNA interference (RNAi). The understanding of RNAi gives scientists the power to “silence” gene expression toward therapeutic ends, and siRNA is one type of RNA molecule used to achieve RNAi. “The real revolution was the discovery that you could make synthetic siRNAs and use them to destroy messenger RNA,” he says. The scientists credited with discovering RNA interference, Andrew Z. Fire, Ph.D., and Craig C. Mello, Ph.D., won the Nobel Prize in 2006.

A dozen years later, the FDA approved Onpattro (patisiran), an siRNA drug, as a treatment for patients with hereditary transthyretin-mediated amyloidosis. The drug was developed by Alnylam Pharmaceuticals. Zamore was a founder of the company, though he no longer works for or consults for Alnylam.

Some RNA therapies work further downstream. RNA aptamers are sticky pieces of RNA that cling to disease-causing proteins. One example is Macugen (pegaptanib), an anti-vascular endothelial growth factor drug used to treat patients with ocular vascular disease.

CLEARING HURDLES

Although there was some early skepticism, plenty of people have been hard at work developing RNA drugs. A 2020 article in Nature counted more than 400 RNA therapeutics, including vaccines, in development pipelines. Most, though, are at early stages of development. Only 3% were in phase 3 trials, and only a handful were awaiting regulatory decisions.

Even as investigators have made progress, Misteli said two persistent problems have perplexed scientists: making sure RNA therapeutics are stable and finding effective means of delivering them to the right place. “The major obstacles at this point are delivery of the RNA agents as well as their stability in cells and tissues as they are relatively rapidly degraded,” he says.

But Zamore says the Pfizer and Moderna vaccines show that subcutaneous administration of RNA therapies can be successful. Earlier therapies, such as Onpattro, required administration by infusion. If the delivery question can be solved, and if the administration route can be simplified, Zamore says RNA therapies could match or even surpass small-molecule drugs, in part because RNA therapeutics’ effects are long lasting. Rather than hoping a patient remembers to take a small-molecule drug every day, physicians might someday be able to prescribe a once-yearly shot.

Zamore also believes RNA therapies will eventually compete with small-molecule drugs on price. The high price tags on the current crop of therapies for the most part are due to generating a return on investment rather than the cost of the goods, he says. As the investment pays off and the techniques for RNA therapies improve, the cost of developing the drugs will drop, Zamore predicts.

“The potential of RNA therapies is more about platforms than specific proprietary products, in Zamore’s opinion. Rather than working on a single small molecule whose applicability may be limited to a single disease, RNA therapy platforms can be leveraged to rapidly develop products for any number of diseases, he says.

That’s a particularly good situation for people like Gordon who have devoted themselves to fighting rare diseases. It means she does not need to rely on persuading a drug company to spend billions of dollars working on progeria, a disease that affects just 1 in 20 million children. Instead, her cause can benefit from RNA therapy research aimed at entirely different disease categories. Gordon says she’s willing to talk and work with anyone who has insights that might help develop new therapies for progeria. “I just want to cure this thing,” she says.

Jared Kaltwasser is a freelance writer in Iowa.
Healthcare disparities, rare diseases and digital therapeutics were among the topics featured at the education sessions of the AMCP Nexus 2021 meeting this week in Denver.

Academy of Managed Care Pharmacy (AMCP) officials said 1,914 people attended the in-person meeting at the Gaylord Rockies Resort and Convention, the first meeting that AMCP has held since AMCP Nexus 2019 meeting in the fall of 2019.

AMCP required attendees to be vaccinated against COVID-19 but also had separate protocol that involved verifying a negative COVID-19 test 72 hours prior the meeting. All attendees were also offered free onsite COVID-19 testing. The meeting had a requirement that people wear masks for indoor activities but from casual observation a large percentage of those in attendance were not wearing masks.

The meeting’s app listed 52 exhibitors. The featured keynote speaker on the second day of the meeting was Sekou Andrews, an inspirational speaker and spoken word artist.

“He had envisioned this meeting as a ‘managed care pharmacy reunion,’ but I didn’t anticipate the electricity that permeated every session and networking experience,” said Susan Cantrell, RPh, CAE, the CEO of AMCP. “It’s a catalyst for the work AMCP is undertaking through our new strategic priorities — optimize value and access, address health disparities, and smart membership growth — to get patients the medications they need at a cost they can afford.”

HOW SCAN HEALTH PLAN TURNED DISPARITY TALK INTO ACTION

It seems like everyone is talking about reducing healthcare disparities, but a pair of SCAN Health executives explained how they got past the talking stage and took concrete steps to reduce disparities in medication adherence.

As described by Sharon K. Jhawar, Pharm.D., MBA, BCGP, chief pharmacy officer of the 220,000-member Medicare Advantage health plan in Long Beach, California, and Timshel Tarbet, MBA, BSP, CCP, vice president of excellence and diversity strategy, some of the notable ingredients of rendering talk into action included a relatively narrow focus (“not boiling the ocean”), creating a health equity dashboard that makes it easy to get disparity-related data and an attitude shift about taking action.

“If we acted, it was one and done and it had to be perfect,” Tarbet. Both Tarbet and Jhawar repeatedly characterized SCAN’s effort to address health disparities as a journey that will require adjustments. “It is a journey — we are learning so much through this process,” Jhawar said. Tarbet also noted that progress in closing the medication adherence gap was a company goal that is tied to compensation: “If we don’t hit it, it affects our paychecks.”

Jhawar and Tarbet shared data showing that there was a 2.9% difference between Black and Latinx members compared with white, Asian and other members on three medication measures. Throughout this year, the difference was smaller and on Oct. 1, it was 1.1%. Medication adherence differences tend to be in single digits; narrowing the gap by 1.8 percentage points is a substantial gain.

Jhawar and Tarbet said SCAN homed in on medication after looking at elements in the CMS Star ratings of health plans and seeing that the plan’s metrics were lower for the Black population overall and that medication adherence metrics were lower for Black and Latinx members. They narrowed the focus even further to medications for diabetes, hypertension and high cholesterol. Jhawar said...
MANAGED HEALTHCARE EXECUTIVE  NOVEMBER 2021

THE DISEASES ARE RARE. THE ORPHAN DRUGS ARE NOT.

The growing ranks of FDA-approved orphan drugs for rare diseases have saved and improved many lives. But the high-priced drugs are also a major cost burden.

Orphan drugs are for rare diseases, but they are becoming a common cost and pharmaceutical management challenge for payers. Magellan Rx Management executives explained at AMCP Nexus 2021.

Favorable tax treatment, lack of FDA user fees, federal research grants and market exclusivity rules have made it attractive for companies to develop orphan drugs, explained Yuqian Liu, Pharm.D., director, specialty clinical solutions at Magellan Rx Management.

In the U.S., orphan drugs are primarily defined as medications for diseases affecting less than 200,000 people.

Liu explain that the same drug may be given orphan drug status by the FDA for several diseases. Conversely, a rare disease may have many orphan drugs approved for its treatment. “We have rare diseases that are getting crowded with products,” she said, citing hemophilia as an example: Liu said there are 30 orphan drug products approved for the disease.

The number of drugs designated as orphan drug by the FDA grew from 132 in 2004 to 335 in 2018. Liu shared pipeline data showing that 33% of applications submitted to the FDA are for orphan drugs and 35% of drugs in phase 3 trials are for orphan drugs. In 2019, the FDA approved 25 new orphan drugs, which accounted for 52% of all approvals, Liu said.

Many of the drugs for orphan diseases have high prices, and Liu said the cumulative effect is a major cost burden on payers. She also illustrated the cost burden of drugs for particular diseases for a hypothetical health plan with a million members. For example, such a plan could expect to have about 15 members with hereditary angioedema that would, as a group, cost the plan $400,000 in drug costs annually. But Liu also noted that plans will see some variation in the patient population with rare diseases. A plan in a region with a center for excellence for hemophilia might, for example, have more than the typical number of people with hemophilia in its membership.

Liu and her colleague, Erin Ventura, Pharm.D., manager, specialty clinical programs at Magellan Rx, also spoke about how plans are attempting to rein in their burgeoning orphan drug costs. Ventura discussed some of the difficulties, which include the absence of treatment guidelines commonly developed for more common disease as such as diabetes and coronary heart disease, and off-label use for the rare diseases that don’t have FDA-approved drugs. Notwithstanding the increasing number of approved drugs for orphan diseases, 95% of rare

Ventura and Liu said experts are often crucial to making formulary and coverage decisions when there is limited data to go on.

Right now, the process in the payer space is that we also look for guidance from the providers in our network, so the key opinion leaders out there, the world-renowned people who are doing the research, who are actually using these drugs to treat patients every day — they are the ones we look to for guidance,” Liu said.

Continued on page 38
Creating member choice and savings through Prime Therapeutics’ channel independent offering

Prime Therapeutics is challenging traditional thinking in the PBM industry with its new MedsYourWay™ offering. This new shopping experience under MedsYourWay gives participating Blue Plans’ members a customer-centric home delivery prescription option using Amazon Pharmacy paired with an integrated MedsYourWay prescription discount card administered by Inside. Purchases of prescribed and covered medications automatically count toward member out-of-pocket maximums. Prime Therapeutics is the first PBM to announce this innovative home delivery option in the marketplace.

Prime Therapeutics is uniquely positioned to offer a variety of solutions; it is not locked into offerings governed by one relationship. Other PBMs may want to drive toward their own home delivery option, but Prime Therapeutics is able to offer what is most cost-effective and convenient for its health plan clients and their members. MedsYourWay represents channel independence and an unbiased approach in identifying the best consumer solutions that allow Blue Plan members easy access to low-cost medications. The first MedsYourWay offering for home delivery using Amazon Pharmacy represents how Prime Therapeutics does business with its Blue Plan partners.

Fast and easy choice for more satisfying user experience
To solve for gaps in the home delivery and drug discount card user experiences, MedsYourWay offers members access to a personalized shopping experience at Amazon Pharmacy where they receive:

- Simplified sign up. Leveraging a seamless data integration that gives members the choice to safely and securely autopopulate their prescription history into Amazon Pharmacy
- Transparency, Savings and Choice. The customer will see the lowest price at Amazon Pharmacy with insurance or the MedsYourWay drug discount card. Depending on the plan, both pricing options for covered medications can accrue (“count”) toward a member’s out-of-pocket maximum. This new pharmacy option is a game changer for members and helps to lower their medicine pricing overall.

- Better than mail order. Convenient home delivery. Once medicine has been ordered, Amazon Pharmacy provides a guaranteed delivery date at checkout and real-time order tracking. Amazon Prime members have the extra benefit of selecting two-day shipping on most Amazon Pharmacy purchases.

Medicines work best when they’re taken as prescribed. A study published in Journal of Managed Care & Specialty Pharmacy showed an estimated 50% improved adherence for consumers using home delivery for their medicines. Through offerings including MedsYourWay, Prime Therapeutics is committed to making it easier for members to get the medicines they need to feel better and live well.

The power of Blue + Prime Therapeutics integration
Blue Plans are actively engaged in the development of MedsYourWay as part of the Prime Therapeutics expansive product innovation discipline. Prime Therapeutics’ clients embrace consumer-focused offerings including MedsYourWay that enable them to deliver a differentiated product to their members. Its model and the actions Prime Therapeutics takes every day on behalf of health plan clients and members demonstrate integration goes beyond pharmacy and medical data to encompass key elements including member experience.

Initially focused on the commercial market, MedsYourWay will be available to Prime Therapeutic’s clients beginning Jan. 1, 2022. Future breakthrough consumer shopping experiences will be launched under the MedsYourWay offering.

JARROD HENSHAW  
Senior Vice President,  
Chief Innovation and  
Supply Chain Officer

As senior vice president, chief innovation and supply chain officer, for Prime Therapeutics (Prime), Jarrod Henshaw sets the vision and provides strategic oversight for trade relations with pharmaceutical manufacturers, network management, pharmacy audit, and fraud, waste and abuse (FWA).

Henshaw comes to Prime with more than 20 years’ experience in the healthcare sector. Prior to joining Prime, he held leadership roles at Healogics, including chief innovation officer, executive vice president of supply chain and chief legal officer. Prior to that, Henshaw spent 14 years at Express Scripts (now Cigna), where he served as chief strategy officer of supply chain and deputy general counsel.

Henshaw earned a Bachelor of Arts degree in political science from the University of Illinois at Urbana-Champaign, Illinois, and a Doctorate of Law from Saint Louis University in St. Louis.

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WHAT’S PROMISING — AND PROBLEMATIC — ABOUT PRESCRIPTION DIGITAL THERAPEUTICS

There are only six currently on the market and eight in late-stage development, but prescription digital therapeutics (PDTs) could usher in an era of value-based contracts, easier collection of real-world evidence and greater access to care, according to members of a panel on PDTs.

But the panelists also discussed possible pitfalls and sticking points for the new therapies, including whether they should be paid for on the pharmaceutical or medical benefit and the lack of standards for supporting evidence that would help payers organize PDTs into formulary tiers.

Pear Therapeutics in Boston, a leading PDT developer that has three therapies on the market, sponsored the Tuesday afternoon session. Yuri Maricich, M.D., MBA, chief medical officer and head of development at Pear and one of the panelists, expressed confidence that patients will use PDTs. “Patients do everything on their mobile devices. They expect they should get treatment on their mobile devices.”

There are thousands of health-related apps that are on the market without FDA approval. The handful of PDTs may have some of the same features and capabilities as a sophisticated app, but they have been approved by the FDA in a category of medical device that requires safety and efficacy evidence from a randomized trial.

Patrick Gleason, Pharm.D., BCPS, FCCP, FAMCP, assistant vice president, health outcomes, at Prime Therapeutics, a PBM owned by Blues plans, and Robert O’Brien, vice president, specialty, at Real Endpoints, a market access consulting firm, were on the panel with Maricich. John Fox, a consultant and president of Foxworthy Healthcare Consulting, was the moderator. Pear and Prime announced in September that they had into entered into a value-based agreement for two of Pear’s PDTs: reSET for substance use disorders and reSET-O for opioid use disorder. Both PDTs provide cognitive behavioral therapy but have safety warnings against being used as stand-alone therapies. Pear and Prime are not disclosing the financial details of their agreement but have announced that some of Prime’s payment for PDTs will hinge on the hospital inpatient stays and total healthcare costs of the patients who are prescribed the PDTs and the physician engagement of the physicians who prescribe it. Prime is making the PDTs and the value-based agreement available to its 23 member Blues plans but it will be up to the individual plans whether to put the PDTs on their formularies.

Gleason talked about the advantages of value-based agreements during the AMCP Nexus 2021 session. How value-based agreements with commercial payers affect a drug’s Medicaid best price has been a sticking point with value-based agreements for drugs but devices are not subject to the best-price rules. “This is the space I finally want to be in,” Gleason. “With drugs you are just so limited on your ability to do value-based contracting because of Medicaid best price.”

Gleason also said the value-based agreements for drugs are complicated and expensive for PBMs and payers because the burden of keeping track of whether a drug is meeting agreed-upon outcomes falls on them “The payer can audit if they are concerned about that the information that is being provided back and fulfillment of the terms of the contract. But it is a lot less of a burden on the payer in value-based contract as result of the way the data is being collected, he said.

O’Brien also expressed enthusiasm about the data the PDTs will generate. “What excites me about this whole space is that the real-world data is going to be flowing much more readily in this space than what we have traditionally seen with drugs or biologics,” he said.

Maricich, whose company also has a PDT for insomnia called Somryst, said the reason the PDTs have been developed for mental and behavioral health is the enormous need and the shortage of treatments. “There is no drug for autism,” he observed. “Thankfully, there is a PDT in development for that.”

Whether PDTs should be seen as druglike and paid for under the pharmacy benefit or as an extension of medical treatment and paid for under the medical benefit is an open question. Gleason made a spirited case for them being paid for on the pharmacy benefit because the coding is specific and would allow payers and PBMs to keep better track of the prescriptions.

Gleason also spoke about payers and PBMs needing more evidence to evaluate PDTs if they are to make coverage and formulary decisions. He referenced an Institute for Clinical and Economic Review report that listed seven possible categories for assessing PDTs: durability of benefit, impact on healthcare utilization, impact on clinician productivity, usability and accessibility for the patient, security, generalizability to diverse population and scalability.
• The first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic

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

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

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

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

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

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

**Immune-mediated colitis:** LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation is 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 or increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

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

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

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

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

Warnings and Precautions (cont’d)

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

Immune-mediated endocrinopathies: (cont’d)

- **Hypophysitis:** LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

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

- **Thyroiditis:** Thyroiditis occurred in 0.6% (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 1.1% 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-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

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

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


REGENERON | SANOFI GENZYME

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

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

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

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

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

4 CONTRAINDICATIONS

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 reintitated 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 reintitated 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 reintitated 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 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Hypophysitis
LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

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

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

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

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 reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hyperthyroidism: Hyperthyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hyperthyroidism led to permanent discontinuation 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 8.3% 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 hyperthyroidism, 1 reinstituted 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 reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

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

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinstituted LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

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

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

Endocrine: Hyperparathyroidism

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

5.2 Infusion-Related Reactions

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

5.3 Complications of Allogeneic HSCT

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.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1 & 8.3)].

6 ADVERSE REACTIONS

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

• Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]

• Infusion-Related Reactions [see Warnings and Precautions (5.2)]

• Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 152 patients with advanced BCs (Study 1620), 355 patients with NSCLC...
and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening 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 laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=350 mg every 3 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, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, pruritus, and confusional state.

The most common (>20%) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. The most common (≥4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hypophosphatemia.

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General and Administration Site</strong></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>34</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
</tr>
<tr>
<td>Rashb</td>
<td>31</td>
</tr>
<tr>
<td>Pruritusc</td>
<td>18</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrheaa</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal paina</td>
<td>24</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough1</td>
<td>14</td>
</tr>
</tbody>
</table>

(continued)
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 1629**

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

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

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

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

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

Toxicity was graded per NCI CTCAE v. 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 pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

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

a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness
b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, and skin reaction
c. Fatigue is a composite term that includes fatigue, asthenia, and malaise
d. Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paracancerous pneumonia, pneumonia, pneumonia bacterial, and pneumonia klebsiella
e. Cough is a composite term that includes cough and productive cough
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 Data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or 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 these patients and younger patients. Of the 219 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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LIB.21.02.0054 02/21
Maintaining optimal levels of low-density lipoprotein (LDL) cholesterol from early adulthood through middle age may reduce the risk of developing coronary heart disease later in life, results of a recent study show.

LDL cholesterol levels usually can be kept low through exercise, a heart-healthy diet and other lifestyle modifications, according to the study’s authors. But for young adults with high LDL levels that don’t respond to lifestyle changes, cholesterol-lowering statin drugs may be necessary.

“For these individuals, pharmacological therapy to lower LDL cholesterol levels earlier in the life course when atherosclerosis is less advanced may be a more successful way to reverse the disease course and prevent future CVD (cardiovascular) events,” Yiyi Zhang, Ph.D., M.S., of Columbia University Medical Center and her co-authors wrote in the September 2021 issue of JAMA Cardiology. If clinicians were to follow their suggestions, many more Americans could be taking statins at a much younger age.

Lowering LDL cholesterol, often by taking a statin, has been a tenet of cardiovascular disease prevention in the United States for decades, but most of the prescriptions are written for older people with a history of heart attack, stroke or another major cardiovascular event.

The editor’s note accompanying the study noted that current hypertension guidelines recommend treating all adults with high blood pressure despite a dearth of evidence that lowering blood pressure in young adults translates into a health benefit. “If the clinical community can support treating hypertension early in life to prevent the long-term risks of elevated blood pressure, the findings in the study by Zhang et al. suggest that a similar paradigm (for cholesterol lowering) should be considered,” wrote Ann Marie Navar, M.D., Ph.D., and Gregg C. Fonarow, M.D., associate editors at JAMA Cardiology.

But the emphasis that has been put on LDL cholesterol levels also has been questioned. Rita F. Redberg, M.D., a cardiologist at the University of California, San Francisco, and editor of JAMA Internal Medicine, has said that an
LDL cholesterol level should be seen as marker of potential cardiovascular disease rather than a target for treatment. Speaking on the Healthy Skeptic MD podcast earlier this year, Redberg said focusing on LDL cholesterol is “misguided.” Instead, she said, doctors should instruct patients to eat a healthy diet and get regular physical activity. “If you have a healthy diet and your cholesterol is high, that’s OK,” she said. “If you have an unhealthy diet and your cholesterol is low, that’s not so good. You really have to focus on lifestyle and stop focusing on lab values.” Redberg also said that the side effects of statins — muscle aches, fatigue — may actually contribute to heart health issues.

By pooling four prospective cohort studies, the study researchers had data from more than 18,000 study participants to evaluate. Using accepted statistical techniques, they calculated the participants’ cumulative exposure to cholesterol levels. The study results suggest that exposure to high levels was associated with a greater likelihood of experiencing coronary heart disease but not stroke or heart failure.

Zhang and her colleagues discussed possible explanations for cumulative high LDL cholesterol levels increasing the likelihood of coronary heart disease. Small particles of LDL cholesterol may lodge inside arterial walls starting in young adulthood. Some research suggests that those retained particles go through various modifications, including oxidation, which can lead to an inflammatory response and vessel failure.

**ALTERNATIVES TO STATINS**

Statins are the go-to medications for lowering LDL cholesterol but there are alternatives, including an yet approved medication that works by interfering with messenger RNA (see page 32) that would be given twice a year as an injection.

But the RNA-oriented medication, inclisiran, which Novartis is selling under the brand name Leqviq, ran aground in the FDA approval process late last year because of problems at the manufacturing facility where the drug is made. In a new application for approval that it filed earlier this year, Novartis said that it had switched the manufacturing of inclisiran to a company facility in Schafftenu, Austria.

Regeneron’s Praluent (alirocumab) and Amgen’s Repatha (evolocumab), both approved in 2015, are also alternatives to statins for some patients. They are monoclonal antibodies that that bind to proprotein convertase subtilisin/kexin type 9 (PCSK9), which has the effect of lowering LDL level by making more LDL receptors on liver cells available. Known as PCSK9 inhibitors, Praluent and Repatha, which are injected once or twice a month, were slow to catch on, partly because payers declined to cover them. The companies ratcheted down the price. After that initial stumble, sales of Repatha have outpaced those of Praluent sales, and Repatha is now approaching blockbuster status — a billion dollars in sales a year. In September, Amgen got more good news when the FDA approved Repatha as a treatment for patients aged 10 years and older with heterozygous familial hypercholesterolemia, an inherited disorder that increases LDL levels. The agency also tweaked its approval of Repatha as a treatment for a different inherited condition, homozygous familial hypercholesterolemia, lowering ages for which it is approved from 13 to 10.

It may be just a matter of time before the FDA approves inclisiran. European drug regulators approved the drug in 2020 and Great Britain’s National Institute for Health and Care Excellence (NICE), which makes cost-effectiveness decisions for the country’s National Health Service, approved it in September 2021. NICE said the drug can be given in primary care settings to patients who have high LDL cholesterol after a previous cardiovascular event. The NICE go-ahead has stirred up controversy because, say the critics, for all of its LDL-lowering prowess, inclisiran hasn’t been shown to reduce cardiovascular events.

But the Institute for Clinical and Economic Review (ICER), the private cost-effectiveness group in Boston, issued a report on inclisiran earlier this year that said that there was “high certainty” that inclisiran would have “at least a small net health benefit with the possibility of a substantial benefit,” partly because its mechanism of action, although novel, is related to Repatha’s and Praluent’s and they have proven positive outcomes. Even so, ICER said inclisiran should have a relatively modest net price of between $3,600 and $6,000 a year.
Seeing LDL cholesterol in a new light

Chronic Disease

Continued from page 49

cular injury and atheroma formation. The accumulated particles, teaming up with circulating LDL cholesterol, may develop atherosclerotic plaque. Thus, keeping LDL cholesterol levels low may prevent that process from starting.

Introduced in 1987, statins are among the most prescribed medications in the world. They are routinely prescribed for patients 55 and older who have had a heart attack or stroke or who have elevated LDL cholesterol levels. Prescribing statins for younger adults was mentioned by the American College of Cardiology and the American Heart Association in their 2019 guidelines on the primary prevention of cardiovascular disease. The guidelines say for young and middle-aged adults, the 30-year and lifetime risk of cardiovascular disease are reasons for reinforcing a lifestyle recommendation and, for some, medication. Still, the vast majority of statin prescriptions are written for older patients. Zhang’s study is far from the final word on prescribing statins for younger people, but it may seed more research and discussion of looking at LDL cholesterol through the lens of lifetime exposure.

Robert Calandra is an independent journalist in the Philadelphia area who writes about healthcare and other topics.

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| 1. Publication Title: MANAGED HEALTHCARE EXECUTIVE |
| 2. Publication Number: 0773 |
| 3. Filing Date: 9-30-21 |
| 4. Issue of Frequency: Monthly |
| 5. Number of Issues Published Annually: 12 |
| 6. Annual Subscription Price: $120.50 |
| 7. Complete Mailing Address of Known Office of Publication (Not Printer): MULTIMEDIA HEALTHCARE LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619 |
| 8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not Printer): MULTIMEDIA HEALTHCARE LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619 |
| 9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor - Publisher: William Mulderry, MULTIMEDIA HEALTHCARE LLC, 485F ROUTE 1 S STE 210, ISELIN NJ 08830-3072; Editor: Laura Joszt, MULTIMEDIA HEALTHCARE LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619; Managing Editor: Peter Wehrwein, MULTIMEDIA HEALTHCARE LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619 |
| 10. Owner - Full name: MULTIMEDIA HEALTHCARE LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619 |
| 11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities: None |
| 12. Publication Title: MANAGED HEALTHCARE EXECUTIVE |
| 13. Issue Date for Circulation Data Below: September 2021 |

| A. Total Number of Copies (Net press run) | 38,877 | 38,003 |
| B. Legitimate Paid and/or Requested Distribution | 20,070 | 23,143 |
| 1. Outside County Paid/Requested Mail | 20,070 | 23,143 |
| Subscriptions stated on PS Form 3541. | 0 | 0 |
| 2. In-County Paid/Requested Mail | 0 | 0 |
| Subscriptions stated on PS Form 3541. | 0 | 0 |
| 3. Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS | 0 | 0 |
| 4. Requested Copies Distributed by Other Classes Mailed Through the USPS | 7 | 9 |
| C. Total Paid and/or Requested Circulation | 17,729 | 23,152 |
| (Sum of 15b, 15c, and 15d) | | |
| D. Nonrequested Distribution (By Mail and Outside the Mail) | 33,040 | 35,003 |
| 1. Outside County Nonrequested Copies | 33,040 | 35,003 |
| Stated on PS Form 3541 | | |
| 2. In-County Nonrequested Copies | 20,077 | 23,152 |
| Stated on PS Form 3541 | 0 | 0 |
| 3. Nonrequested Copies Distributed Through the USPS by Other Classes of Mail | 0 | 0 |
| 4. Nonrequested Copies Distributed Outside the Mail | 0 | 0 |
| E. Total Nonrequested Distribution (Sum of 15e, 15f, and 15g) | 17,723 | 23,152 |
| (Sum of 15f and 15g) | | |
| F. Total Distribution (Sum of 15a and 15e) | 30,800 | 34,992 |
| G. Copies not Distributed | 40 | 11 |
| H. Total (Sum of 15f and 15g) | 33,840 | 35,003 |
| I. Percent Paid and/or Requested Circulation | 55.49% | 66.15%

16. If total circulation includes electronic copies, report that circulation on lines below

a. Requested and Paid Electronic Copies | 1,863 | 2,315 |
| b. Total Requested and Paid Print Copies + Requested/ Paid Electronic Copies | 21,940 | 25,467 |
| c. Total Requested Copy Distribution + Requested/ Paid Electronic Copies | 35,663 | 37,307 |
| d. Percent Paid and/or Requested Circulation (Both print & Electronic Copies) | 61.52% | 68.26%

17. Publication of Statement of Ownership – Will be printed in November 2021 issue of this publication.

I certify that all information on this form is true and complete.

Signature and title of Editor, Publisher, Business Manager, or Owner –
Jonathan Severn, Circulation Director, 9-29-21
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For decades, cancer treatment drugs have been infused either at a hospital or in a physician-owned office or facility. For patients, the treatments were inconvenient and time consuming, to say nothing of the onslaught of side effects. Cancer treatment is still a trying experience. Harsh chemotherapies remain in the armamentarium, although oncologists now have agents to better manage some of their side effects, notably nausea. But cancer treatment has also changed dramatically with many more oral formulations that can be taken at home and new opportunities to deliver infusions at home, partly due to the emergence of telehealth. For the most part, patients have benefited. But the changes have set off a struggle among hospitals, oncologists and providers about which patients are going to be treated where and by whom.

Payment for home infusions is still evolving, as is the medical community’s enthusiasm for it. Medicaid, the ACA exchange and commercial health plans are proving grounds. The Community Oncology Alliance and the American Society of Clinical Oncology have both raised concerns about patient safety.

Hospitals vs. physician offices
Home infusion is coming on strong, but most infusions still occur in a medical setting. Hospitals and oncologists have been battling over infusion patents for years, and there’s ample evidence that where the infusion takes place has a large effect on its price. Research findings published in the September 2021 issue of Health Affairs adds to that pile.

James C. Robinson, Ph.D., M.P.H., a professor of health economics at the University of California, Berkeley, and his colleagues had access to a claims database that includes 130 million Blues plans members. Their analysis of claims in 2019 found that the prices the plans paid at hospital outpatient departments for 38 infused cancer treatment drugs were double the prices paid at physician offices. It’s not surprising that there is a difference, but the research documented it and showed how large it can be.

"Moving care from high-cost, hospital-based settings to lower-cost ambulatory settings is the lowest-hanging fruit in healthcare cost control," Robinson said in an interview with Managed Healthcare Executive. "This goes for drug infusions but also surgical and diagnostic procedures, in cancer and other forms of care."

Robinson noted that technology has made it possible to deliver many drug treatments outside the hospital, but hospitals have purchased many of the outpatient centers and physician offices — and then raised the price of care delivered there. "This vertical integration rivals horizontal integration through mergers in explaining high (healthcare) costs," he said.

In their Health Affairs article, Robinson and his colleagues, Christopher M. Whaley, Ph.D., a RAND health economist, and Timothy T. Brown, Ph.D., associate director for research of the Berkeley Center for Health Technology, note that health plans have combated high prices at hospitals with narrow network strategies — essentially, refusing to reimburse at the higher-priced settings. They calculated that a full-blown narrow network strategy for the infused drugs included in their study would have generated $1.28 billion in savings, or about a quarter of what the Blues plans
spent on the medications. Narrow networks have drawbacks, though. They limit patient choice and can lead to surprise billing when patients inadvertently get care out of network.

Patients also shoulder some of the cost of infused cancer drugs because of deductibles and cost sharing: Robinson, Whaley and Brown discovered an odd twist when they looked at what the Blues plans’ patients paid in 2019. Despite much higher prices paid by the plans at the hospital outpatient departments, they found that the patient cost sharing was less, not more, at the hospital outpatient departments than at physician offices for 25 of the 38 drugs included in the study.

Strategies like uniform coinsurance (patients pay the same percentage of the cost regardless of the setting) and reference pricing (patients pay the difference between the price at the lowest-priced setting and the price at the setting where they are receiving care) are designed so patients have a financial disincentive to avoid high-cost settings. But such strategies open the possibility that patients will shoulder more of the cost of expensive cancer medications.

Robinson, Whaley and Brown put it this way in Health Affairs: “Substantial savings are potentially available to them with this shift in care, but consumer cost-sharing strategies can impose very large financial burdens on patients.”

**Home infusion thickens the plot**

There’s no end in sight to hospital and physicians vying to take care of cancer patients. But home infusion is a relatively new development that challenges both. “For home-appropriate chemotherapy agents, which include monoclonal antibodies, clinical oversight can be provided by a nurse on-site during the infusion, with telemedicine providing connectivity to the oncologist,” says Andrew Hertler, M.D., chief medical officer of New Century Health, a specialty managed care company owned by Evolent Health. It’s often advisable that an initial infusion or two first be given in a clinical setting to ascertain patient tolerance, observes Hertler.

Still, many oncology practices have relied on revenues from drug infusions, so home infusion looms as a threat and the increasing number of oral formulations perhaps more so. But Hertler says it’s possible to design payment models that realign reimbursements to pay oncologists for oversight and remove this disincentive. Although home infusion may be a major convenience for patients, for practices it has some built-in inefficiency, says Hertler: “In the clinic, a nurse can oversee several patients’ infusions at once. At home, it is one to one. Drug savings have to make up for the increase in manpower.” Telehealth may help offset some of the efficiency problems.

Physician assistants and nurse practitioners are another factor in how and where cancer treatment will be delivered in the future. As their numbers increase, so may the home-based care they can deliver that oncologists can’t because their time is too valuable and in short supply. “Going forward, I envision that each oncologist will provide oversight of several extenders — physician assistants and nurse practitioners — who will provide the actual patient care much of the time,” Hertler says. “Oncology will move to a team approach rather than the current model of each oncologist seeing every patient one-on-one. The oncologist will become more of a quarterback directing the team.”

Hertler also envisions artificial intelligence playing a futuristic role in oncology, affecting much more than the site of service. “An oncologist’s skill set involves interpreting data collected from pathology, imaging, laboratory, history and exam reports and recognizing a pattern, which leads to selection of the treatment plan most likely to work based on those many variables,” Hertler says. “AI and decision support is quite simply going to become better than the oncologist at this, never missing an input or making a mistake. Quite frankly, my skill set as an oncologist will become obsolete.”

Keith Loria is a freelance writer in the Washington, D.C., area.
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On being new to the PBM industry

Coming into this job, I knew very little about pharmacy and the PBM industry and how it worked and the machinations and dynamics of the industry. So you just have to put it in perspective: I’m not a deep, PBM-industry guy. That, surprisingly, has been very helpful to my work — the fact that I’m coming at it from a fresh perspective. And I can look at it and say, “Well, here’s the things I like about the industry” — and we’re doing a lot of good. And I never really understood it until now. And then I’d say, “Maybe some of the ways in which we do the work probably could be improved.”

On the reputation and value of the PBM industry

I can tell you now that I’ve been in this seat for two years, the counterweight, the counterbalance activity of the PBMs in healthcare — it’s incredibly important. It’s literally in the billions and billions of dollars of savings that the PBM industry provides to healthcare through this counterbalance to Big Pharma. Without that counterbalance, I’ve got to tell you that healthcare would be a lot more expensive in this country. So I’m convinced that there’s value there — and I wouldn’t do the job if I didn’t think there was.

On transparency

The opacity of the industry, the complexity of it, is nothing short of stunning. I mean, to follow the funds flow of dollars that come from the top and work all the way through the industry down to the bottom — to the member and whatnot, and even providers, in some ways — is incredibly complicated. It did take me a few months to unravel all that. And I do often ask myself the question “why does have to be so complicated?” And I don’t think it does.

On rebates

But it’s important to remember where rebates came from, and, actually, it’s a model that pharma initially promoted — that we’re going to give you a discount, but only if you move market share, and the discount will be in the form of a rebate, because we don’t want to pay it unless you actually move share. So we all have to remember that the whole rebate model started with pharma pushing for market share. I totally understand it, and I get it, and I support it.

Where it became complex was when the PBM industry (began) taking pieces of those rebates as a funding stream. PBMs need to have their costs paid for. I think that’s reasonable. If you do it through spread pricing — take a piece of the rebates — or you do it through an admin fee or some combination thereof, I’m OK with those costs being reimbursed. The question is “can we do it in a way that’s really
Chronically and critically ill patients often need acute care after their stay in an intensive care or medical/surgical unit. While these medically complex patients make up a small part of overall care delivery, it is critical to identify the appropriate care setting for them in order to decrease the risk of costly rehospitalization.

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understandable to the system and to the industry and to members — and to doctors, for that matter? And I think we can.

But (they) get a bad name, I think mostly because of the opacity and complexity.

On the switch from provider organizations to a PBM
I come from a family of caregivers. I’m one of six. There’s a physician — my older brother is a primary care doc, my older sister is an occupational therapist, I was three, the fourth is a Ph.D., N.P. mental health clinician. The fifth is a psychologist, and the last one is a counselor.

So I come from a provider family, if you will, and I tell you, when I moved from working in hospitals and clinics to working at a PBM, they were very concerned — to say the least.

The fact of the matter is, there’s really an important role for both. The provider side — I always appreciated it, because you’re right in the middle of the action: “Are we doing the right thing for patients?” What we weren’t good at was “are we doing the right thing for patients in a way that is affordable?”

And that’s where we come in. So we bring the affordability to the table, I think, in some ways, and the providers bring the care and the quality to the table.

On the separation of pharmacy management from medical management
It just boggles my mind that we would separate pharmacy out and manage it off to the side and medical care be managed over here, and the two don’t meet. That absolutely makes no sense to anybody.

It’s almost the same conversation where we used to separate behavioral health and mental health from physical health. It makes no sense.

So I am driven to drive these two worlds back together. Bring the provider back into the equation, have he or she be part of the solution — all of us together in service of the patient. And if we do that, affordability will follow.

On Prime’s independence from Express Scripts
The beauty of the relationship is we didn’t really hand over the keys. Unlike Adam’s* perspective on this, we didn’t really change anything at Prime other than that.

We still process our own claims. We own the claim system. We do all our own PAs, (prior authorizations) contact center, utilization management — we do everything ourselves. But that piece sits off behind the scenes and then feeds our systems.

So it’s been a fairly elegant solution for us as a way to save significant dollars for clients and members and employers, but to do so without giving up our strategic optionality, which is continuing to run our own business.

*Adam Fein is an influential expert on drug distribution and pricing. Fein has written about what he sees as Prime’s increasing reliance on Express Scripts.