A review of systemic lupus erythematosus and current treatment options

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Focus on bazedoxifene
An investigational selective estrogen receptor modulator for the treatment and prevention of osteoporosis in postmenopausal women

Diana M. Sobieraj, PharmD
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Medication Safety and Reliability
FDA cautions prescribers of risk for severe immune-mediated adverse reactions with ipilimumab use

Drug Watch
Agents in late-stage development for major depressive disorder and generalized anxiety disorder

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Editorial Mission

To provide timely, accurate, and practical drug-related information to assist our readers in their drug management responsibilities—evaluating drugs for the formulary and developing policies and procedures to guide the appropriate, rational, safe, and cost-effective use of drugs.

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Cover Article

A review of systemic lupus erythematosus and current treatment options

Allison Bernknopf, PharmD, BCPS; Kristina Rowley, PharmD, CDE; Teresa Bailey, PharmD, BCPS, FCCP

178 Systemic lupus erythematosus (SLE) is an autoimmune disorder that affects multiple organ systems including the skin, kidneys, and brain. The exact cause is unknown but genetic factors, ethnic origin, environmental factors, and medications may all be involved in its development. Women, African-Americans, and Hispanics are more likely to develop SLE. Earlier diagnosis and more effective treatment options have significantly improved 5-, 10-, and 20-year survival rates. Nonpharmacologic treatment is limited and mainly involves proper sun protection—avoidance, protective clothing, and sunscreen. Pharmacologic treatment is usually tailored to the specific symptoms or organ systems that are involved. Treatment modalities include steroids, antimalarials, and cytotoxic/immunosuppressive agents. This review will examine the clinical course of SLE, various treatment options, and the treatment of specific manifestations of the disease such as lupus nephritis.

Focus on...

Bazedoxifene: An investigational selective estrogen receptor modulator for the treatment and prevention of osteoporosis in postmenopausal women

Diana M. Sobiera, PharmD; Stefani C. Nigro, PharmD, C-TTS

159 Bazedoxifene is a selective estrogen receptor modulator under investigation for the treatment and prevention of osteoporosis in postmenopausal women. In phase 3 trials, bazedoxifene-treated patients with normal to low bone mineral density (BMD) had significantly higher BMD at the lumbar spine and hip, which was similar to patients treated with raloxifene. In patients with osteoporosis, bazedoxifene significantly decreased the risk of vertebral fractures as well as nonvertebral fractures in a subgroup of high-risk patients. The most common adverse events reported in phase 3 trials were headache, infection, arthralgia, pain, hot flushes, back pain, abdominal pain, accidental injury, flu syndrome, and hypertension. Bazedoxifene-treated patients had a high incidence of hot flushes versus placebo, but this was similar to raloxifene-treated patients. Bazedoxifene is unlikely to interact significantly with other drugs due to its metabolism via glucuronidation and currently does not appear to require dose adjustment for renal or hepatic impairment.

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New molecular entities

Edarbi
Azilsartan medoxomil
TAKEDA PHARMACEUTICALS AMERICA

A new angiotensin receptor antagonist for the treatment of hypertension

Hypertension impacts approximately 74.5 million Americans, or nearly 1 in 3 adults. Recent estimates from the American Heart Association suggest that the cost of hypertension in the United States, including both direct and indirect costs, exceeded $76 billion in 2010. Azilsartan medoxomil 40 mg and 80 mg tablets were approved by FDA for the treatment of hypertension, either alone or in combination with other antihypertensive agents.

Azilsartan is a selective AT1 subtype angiotensin II receptor antagonist that lowers blood pressure by blocking the action of angiotensin II, a vasopressor hormone that constricts blood vessels.

Efficacy. The antihypertensive efficacy of azilsartan was evaluated in a total of 7 randomized, double-blind trials. Of note, two 6-week, randomized, double-blind trials compared azilsartan 40 mg and 80 mg to placebo, olmesartan 40 mg, and valsartan 320 mg. Compared to placebo, azilsartan lowered systolic and diastolic blood pressure by up to 15.5 mmHg and 8.6 mmHg, respectively, when measured during clinic visits, and by as much as 14.3 mmHg and 9.4 mmHg, respectively, upon use of 24-hour ambulatory blood pressure monitoring.

Most of the antihypertensive effect seen with azilsartan occurred within the first 2 weeks of treatment. When compared to active controls, azilsartan 80 mg daily was found to be statistically superior to the highest FDA-approved doses of olmesartan and valsartan upon both clinic and 24-hour ambulatory blood pressure monitoring.

Safety. Nearly 5,000 patients taking azilsartan (at doses between 20 mg and 80 mg) were evaluated for safety end points during clinical trials. This included 1,704 patients treated for at least 6 months and 588 for a minimum of 1 year on azilsartan. Diarrhea (2%) was the most common adverse effect seen in patients during clinical trials. Other adverse effects (occurring in ≥0.3% of patients and more often than placebo) included: dizziness, cough, asthenia, fatigue, and muscle spasm. As with all approved angiotensin receptor antagonists and other medications that act directly on the renin-angiotensin system, use during pregnancy can result in fetal injury and death and is contraindicated.

Dosing. The recommended dose of azilsartan in adults is 80 mg once daily with or without food. No initial dose adjustment is recommended for elderly patients, patients with mild-to-severe renal impairment, end-stage renal disease, or mild-to-moderate hepatic impairment (not studied in severe hepatic dysfunction). It is recommended however, that prescribers consider a lower starting dose of 40 mg in patients with volume or salt depletion, including patients concomitantly treated with higher doses of diuretics.

Daliresp
Roflumilast
FOREST

A novel oral treatment to reduce the risk of COPD exacerbations in patients with severe COPD

According to the National Heart, Lung and Blood Institute, mortality due to chronic obstructive pulmonary disease (COPD) is on the rise and currently the fourth leading cause of death. It is estimated that 12 million Americans have been diagnosed with COPD, and an additional 12 million have the disease but are unaware. On March 1, 2011, roflumilast was approved by FDA as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (not the relief of acute bronchospasm). While the exact mechanism of action of roflumilast and its active metabolite (roflumilast-N-oxide) is not completely understood, it is hypothesized that its pharmacologic effect is a result of selective inhibition of phosphodiesterase 4, which leads to accumulation of intracellular cyclic adenosine monophosphate in lung cells.

Efficacy. The efficacy of roflumilast 500 μg once daily in patients with COPD was evaluated in four 1-year long randomized trials. Initial placebo-controlled trials enrolled patients with severe COPD (inclusive
of those with chronic bronchitis and/or emphysema) and a history of smoking of at least 10 pack-years. These trials failed to demonstrate significant reductions in the rate of COPD exacerbations with roflumilast. However, 2 subsequent randomized trials enrolling patients with severe COPD associated with chronic bronchitis, at least 20 pack-year smoking history, and at least 1 COPD exacerbation in the previous year (eg, overall sicker patients) were able to demonstrate statistically significant (15% to 18%) relative reductions in the risk of COPD exacerbations. Improvements in forced expiratory volume in 1 second (FEV1) of approximately 50 mL also were seen.

**Safety.** In randomized clinical trials lasting between 6 months and 1 year, 14.8% of patients receiving roflumilast discontinued therapy due to adverse reactions (compared to 9.9% of placebo-treated patients). The most common adverse reactions seen with roflumilast (occurring in ≥2% of patients) were diarrhea (9.5%), weight decrease (7.5%), nausea (4.7%), headache (4.4%), back pain (3.2%), influenza (2.8%), insomnia (2.4%), dizziness (2.1%), and decreased appetite (2.1%). During clinical trials, roflumilast use was found to be associated with an increased incidence of psychiatric adverse reactions. Three cases of suicidal ideation and behavior (1 resulting in death) were seen in patients taking roflumilast. Other serious adverse reactions of note (occurring more frequently in roflumilast-treated patients) included atrial fibrillation, lung and prostate cancer, acute pancreatitis, and acute renal failure.

**Dosing.** The recommended dose of roflumilast in patients with COPD is 500 μg once daily taken with or without food. No dose adjustment is needed based upon age, gender or race, nor is it required in patients with renal impairment. While roflumilast has not been studied in hepatically impaired patients, based upon pharmacokinetic studies, it is recommended that clinicians consider both the risks and benefits of administering the drug prior to prescribing it to patients with mild liver impairment. Roflumilast is not recommended for use in patients with moderate or severe liver impairment.

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**Tocilizumab (Actemra, Genentech)** given alone or in combination with methotrexate, was approved for the treatment of active systemic juvenile idiopathic arthritis in children aged 2 years and older.

Meningococcal conjugate vaccine (Menactra, Sanofi Pasteur), (meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine), was approved to expand the indication to include a 2-dose schedule for infants and children aged 9 months through 23 months of age. This is the first US approval of a meningococcal vaccine for this age group.

Abiraterone acetate (Zytiga, Centocor Ortho Biotech) in combination with prednison was approved to treat patients with metastatic castration-resistant prostate cancer who have received prior docetaxel.

Rituximab ( Rituxan, Genentech), in combination with glucocorticoids, was approved to treat patients with Wegener’s granulomatosis and microscopic polyangiitis, 2 rare disorders that cause vasculitis.

Paliperidone (Invega, Janssen Division of Ortho-McNeil-Janssen Pharmaceuticals) extended-release tablets were approved for the treatment of schizophrenia in adolescents aged 12 to 17 years old.

Vandetanib (AstraZeneca) was approved for the treatment of symptomatic or progressive medullary thyroid cancer in patients with non-operable locally advanced or metastatic disease.

Nevirapine (Viramune XR, Boehringer Ingelheim) single-pill, once-daily, extended-release antiretroviral for use in combination with other antiretroviral drugs was approved for HIV-1 adult patients.

Gabapentin enacarbil (Horizant, GlaxoSmithKline and XenoPort) extended-release tablets were approved for the treatment of moderate-to-severe primary restless legs syndrome in adults.
Genetic targets help alcohol addiction, study finds

By Barbara Hesselgrave

Alcoholics who are tested for genotype specificity prior to receiving ondansetron may have significantly improved outcomes, according to a report published in the March 2011 issue of American Journal of Psychiatry.

In a double-blind controlled trial, a cohort of 283 people with alcohol addiction were randomized by their specific genotype of the serotonin transporter gene: the 5’-regulatory region of the 5-HTT gene (LL/LS/SS) and a polymorphism in the 3’-untranslated region. Study subjects were given either ondansetron (4 μg/kg twice daily) or placebo for 11 weeks, and also received cognitive behavioral therapy. People with the LL genotype who received ondansetron reported a lower mean number of drinks per drinking day (-1.62) and a higher percentage of days abstinent (11.27%) than participants who received placebo. Individuals with non-LL genotype patterns receiving ondansetron responded less favorably than the LL group.

Results from this investigation demonstrate the direct relationship of an alcohol addiction patient’s genetic profile and his/her ability to respond to therapy. Based on the results of their study, investigators “propose a new pharmacogenetic approach using ondansetron to treat severe drinking and improve abstinence in alcoholics.”

The study further confirms the benefits of genetic targeting for drug therapies, according to lead investigator Bankole A. Johnson, MD, PhD, DSc, chairman of the department of psychiatry and neurobehavioral sciences at the University of Virginia School of Medicine, Charlottesville, Va.

“One side of targeting treatment is tailoring the efficacy of response, that is, giving medicine to people who respond to the medication. The other side of this approach is to have no side effects and no adverse events,” said Dr Johnson.

From a payer perspective, Dr Johnson said, “Even if you look at the most successful psychiatric drugs, not much more than half of the people taking a medicine, sometimes less than that, respond to it. This is a huge waste in medical costs, hospital costs, drug expense, and it doesn’t help patients.”

Source


New treatment guidelines strongly endorse use of biologic agents for many children with arthritis refractory to methotrexate

Fueled by major changes over the last decade in the treatment of juvenile idiopathic arthritis (JIA), including the introduction of biologic therapeutic agents, the American College of Rheumatology (ACR) has developed new guidelines for starting and monitoring treatments for children with JIA. These are the first JIA guidelines endorsed by the ACR, with the goal of broad acceptance within the rheumatology community.

The research team, led by Timothy Beukelman, MD, MSCE, an ACR member, and assistant professor of pediatrics in the division of pediatric rheumatology at the University of Alabama at Birmingham, developed the guidelines using established processes from the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method. The method defines appropriate patient care by combining the best available scientific evidence with the collective judgment of experts.

The guidelines focus on the initiation and safety monitoring of multiple medications used in the treatment of JIA, including:

- Nonsteroidal anti-inflammatory drugs (eg, ibuprofen, naproxen, and many others)
- Intra-articular glucocorticoid injections (ie, steroid joint injections)
- Nonbiologic disease-modifying antirheumatic drugs (eg, methotrexate)
- Biologic disease-modifying antirheumatic drugs (eg, abatacept, anakinra, and TNF-α inhibitors such as etanercept, adalimumab, infliximab)
- Systemic glucocorticoids (eg, prednisone)

Chronic childhood arthritis is a heterogeneous condition, said Dr Beukelman.

“The most recent classification of JIA uses 6 distinct categories. However, the treatment of JIA is not currently influenced by some of the distinct categories of JIA. For example, there are not specific therapies directed at psoriatic arthritis as opposed to oligoarthritis or RF [Rheumatoid factor]-negative polyarthritis,” he told Formulary.
“Accordingly, we developed JIA ‘treatment groups’ for the recommenda-
tions based on important phenotypic differences in JIA. The 5 treatment
groups are history of arthritis of 4 or fewer joints, history of arthritis of 5 or
more joints, active sacroiliac arthritis, systemic arthritis with active systemic
features, and systemic arthritis with active arthritis.”

The treatment of JIA has changed dramatically over the last decade, Dr
Beukelman explained. “The ACR recommendations provide evidence and
consensus-based guidance that reflects the current state of the field. These
recommendations endorse the use of bio-
logic therapeutic agents for children with
JIA whose arthritis remains active de-
spite treatment with methotrexate. These
recommendations are not intended to be
used to determine insurance coverage
policies, but my personal hope is that the
recommendations will result in increased
access to appropriate treatment.”

The most notable recommenda-
tions regarding the use of biologic
agents include the initiation of
TNF-α inhibitors for children with
a history of arthritis of 4 or fewer
joints if significant arthritis proves
refractory to methotrexate.

In addition, Dr Beukelman continued,
“for children with a history of arthritis of
5 or more joints, the initiation of TNF-α
inhibitors is recommended for essentially
all patients with any active arthritis fol-
lowing an adequate trial of methotrexate.
Finally, for children with systemic
arthritis who require a steroid-sparing
agent because of active fever, initiation of
anakinra is recommended,” he said.

In the development of the recom-
mandations, Dr Beukelman and the re-
search team, which included clinicians,
researchers, and a patient advocate,
performed a systematic review of the
literature that identified more than 200
studies of the treatment of JIA. “These
studies were abstracted and compiled
into an evidence report that was pre-
sented to our voting panel,” Dr Beukel-
man explained. “We also evaluated
more than 1,500 clinical scenarios that
captured the complexity of treatment
decisions in JIA, including the JIA
treatment group, disease activity, pres-
ence of features of poor prognosis, and
current medications. The voting panel
then considered the scenarios based on
the published literature or their own ex-
pert opinions when sufficient evidence
was not available.”

It is estimated that 1 child in every
1,000 will develop a rheumatic disease. Nearly 300,000 American children
suffer from JIA, which begins before
patients reach aged 16 and may involve
chronic inflammation of 1 or many
joints. JIA often persists into adulthood
and can cause long-term coexisting
conditions and disability.

Source
Beukelman T, Parkar NM, Saag KG, et al. 2011
American College of Rheumatology recommenda-
tions for the treatment of juvenile idiopathic arthri-
tis: initiation and safety monitoring of therapeutic
agents for the treatment of arthritis and systemic

Shorter treatment for HCV may be possible with protease inhibitor

Analysis of the hepatitis C virus (HCV) kinetics during treatment with protease
inhibitor telaprevir shows a rapid viral
decline, which could allow for shorter
treatment, according to a study published
online in *Hepatology*.

Chronic HCV infection has a world-
wide prevalence of about 3%. Achieving
a long-term sustained virologic response
(SVR), defined as undetectable HCV
RNA in serum 24 weeks after the end
of treatment, is the most effective way
to prevent disease progression. Currently,
treatment outcome with pegylated
interferon and ribavirin is correlated
with HCV genotype and SVR is only
achieved in half of HCV genotype 1
patients, the most prevalent genotype in
western countries.

Researchers Jeremie Guedj, PhD, and
Alan S. Perelson, PhD, from the Los
Alamos National Laboratory in New
Mexico, examined HCV viral decline
during treatment with telaprevir.

“The basic idea of the paper was to
mathematically describe the viral load
kinetics of decline in the first 2.5 days
of treatment in 44 HCV genotype 1
patients treated with various regimens of
telaprevir,” Guedj told *Formulary*. “Us-
ing the viral kinetic parameters found in
this group of patients during this short
period of time as a representative sample
of naïve genotype 1 patients under
telaprevir therapy, and assuming that
drug resistance can be avoided, we could
estimate the treatment time needed to
eliminate all virus and infected cells.”

The researchers found that the
second-phase viral decline was associ-
ated with the effectiveness of treatment,
and was about 4 times more rapid with
telaprevir than interferon-based therapi-
es. Also the viral kinetics were consis-
tent across patients and dosing-group
regimen and did not reveal variations as
large between patients as when treated
with the standard of care.

“We determined that, if resistance
could be avoided and assuming full
compliance to treatment, 7 to 10 weeks
of treatment would be sufficient to clear
HCV with telaprevir in 95% of patients,”
Guedj said. “This result may drive
future clinical trials. However to attain
SVR in 95% of treatment-compliant
patients with a 10-week course of
therapy will require treatments with 3 or
more direct-acting antivirals including
ribavirin. Clearly, at present there are no
approved regimes that meet our crite-
ria of high potency and a high enough
barrier to resistance.”

Source
Guedj J, Perelson AS. Second phase HCV RNA
decline during telaprevir based therapy increases
*Hepatology*. 2011;Mar 7 doi:10.1002/hep.24272
[Epub ahead of print].

Continued from page 157
Bazedoxifene: An investigational selective estrogen receptor modulator for the treatment and prevention of osteoporosis in postmenopausal women

Diana M. Sobieraj, PharmD
Stefanie C. Nigro, PharmD, C-TTS

Defined as a skeletal, degenerative bone disease, osteoporosis affects an estimated 10 million persons in the United States.1 An additional 34 million US adults are at risk for developing the disease due to osteopenia. Although prevalent in various patient populations, most cases of osteoporosis occur in postmenopausal women, and prevalence increases with age.2 Estrogen deficiency after menopause is a major contributor to the development of osteoporosis and leads to an imbalance between osteoclast and osteoblast activity.3 Accelerated bone loss increases the risk of fractures, most notably those of the hip. Osteoporotic fractures account for substantial healthcare costs, disability, and mortality.1

The National Osteoporosis Foundation supports the importance of lifestyle modifications, such as weight-bearing exercise, tobacco cessation, and supplementation with calcium and vitamin D to help slow disease progression.4 Drug therapy also plays a pivotal role in both the prevention and treatment of osteoporosis when indicated. Recommended therapies include estrogen supplementation, bisphosphonates, recombining parathyroid hormone, calcitonin, and selective estrogen receptor modulators (SERMs).1,2

SERMs are a heterogeneous class of compounds that exert their pharmacologic effects at estrogen receptors (ERα and ERβ).3 Currently, SERMs that are FDA approved for use include tamoxifen and raloxifene. These compounds differ from each other in their ability to act as either agonists or antagonists in a tissue-specific manner. Tamoxifen, a triphenylethylene derivative, is indicated for the treatment of breast cancer in pre- and postmenopausal women.4 Raloxifene, a benzothiopene derivative, is approved for the prevention and treatment of postmenopausal osteoporosis.5 Although raloxifene’s effects on bone and lipids are well established, raloxifene induces both vasomotor symptoms and vaginal atrophy that may lead to treatment discontinuation.3 A new SERM, bazedoxifene acetate, is currently under development in an effort to maximize potential benefits on bone, lipids, and breast tissue while minimizing endometrial hyperplasia and other adverse effects.6,7 Such advancement in drug development may expand frontline treatment options for postmenopausal osteoporosis.

CHEMISTRY AND PHARMACOLOGY

Bazedoxifene acetate (1H-Indol-5-ol, 1-[(4-[2-(hexahydro-1H-azepin-1-yl)ethoxy]phenyl)methyl]-2-(4-hydroxyphenyl)-3-methyl, WAY-140424) is a nonsteroidal, indole-based estrogen receptor ligand.6,8,9 Structurally, bazedoxifene resembles raloxifene, but differs by substitution of an indole ring for the benzothioprine core.8,10 Within the class of SERMs, chemical differences in the location and structure of side chains determine...
tissue selectivity, pharmacologic action, and lead to a mixed functional activity at the estrogen receptors. Bazedoxifene binds to both ERα and ERβ with higher affinity toward ERα. Compared to raloxifene, bazedoxifene is less selective for ERα (IC_{50} 26nM) and is about 10-fold lower than 17β-estradiol (IC_{50} 3.2nM). Bazedoxifene exerts pharmacologic activity by binding to estrogen receptors in bone tissue as an agonist promoting preservation of bone mineral density (BMD). At breast and uterine tissue, bazedoxifene acts as an antagonist, therefore lacking stimulation and proliferative activity within these tissues.

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Single- and multiple-dose pharmacokinetic (PK) studies of bazedoxifene have been completed in healthy, postmenopausal women. After administration of multiple doses of bazedoxifene 5 mg/d, 20 mg/d, or 40 mg/d for 14 days, maximum concentration in serum (C_{max}) was 1.6+0.5 ng/mL, 6.4+2.4 ng/mL, and 12.5+5.1 ng/mL, respectively. Maximum concentration in serum is reached within 1 to 2 hours of administration. The absolute bioavailability of oral bazedoxifene is approximately 6.2%; this is 3 times the bioavailability compared with other SERMs on the market, including raloxifene. Concentration-time profiles of capsule and tablet formulations are similar, suggesting both oral formulations are bioequivalent with respect to the area under the concentration time curve (AUC). Bazedoxifene also demonstrates linear pharmacokinetics when dosed from 5 mg to 40 mg daily.

The elimination half-life of bazedoxifene is approximately 28 hours. Steady-state concentration is achieved 7 days after administration. Bazedoxifene is highly protein bound (>99%) and demonstrates a volume of distribution of 248+134 L/kg. Bazedoxifene exhibits little to no cytochrome P450 activity, which may minimize potential for drug-drug interactions. The major metabolic pathway of bazedoxifene is via glucuronidation. Bazedoxifene-5-glucuronide is the primary metabolite (40%-95%) responsible for the majority of circulating radioactivity. The major route of excretion is via the feces (84.7%) with only a minor amount (0.81%) excreted in the urine.

**CLINICAL TRIALS**

The efficacy of bazedoxifene for the treatment and prevention of postmenopausal osteoporosis has been reported in 4 clinical trials (two phase 2 and two phase 3 trials). In addition to measuring fracture risk and BMD, markers of bone turnover are often evaluated to help understand mechanism of action. Osteocalcin and serum type I collagen C-telopeptide (CTX) are markers of bone formation and resorption, respectively, used in bazedoxifene trials. For example, antiresorptive therapies cause a decrease in both markers of bone formation and resorption while the opposite is true of anabolic therapies such as parathyroid hormone.

**Phase 2 trials.** The first phase 2 trial evaluated the effects of bazedoxifene on markers of bone turnover. This trial was prospective, randomized, and double-blind comparing bazedoxifene 5 mg, 10 mg, and 20 mg to raloxifene 60 mg or placebo. A total of 494 healthy postmenopausal women were enrolled and treated for 3 months. Investigators reported a dose-related reduction in bone markers in the bazedoxifene and raloxifene groups versus placebo, with doses as low as 5 mg of bazedoxifene.

The second phase 2 trial evaluated the endometrial effects of bazedoxifene. Women aged 40 to 65 years, at least 12 months post menopause, and within 10 years of last natural menstrual period, with a follicle-stimulating hormone level in the postmenopausal range, BMI ≤35 kg/m², and increased bone turnover as measured by urinary N-telopeptide were included. Subjects were excluded if they had known or suspected acute or uncontrolled chronic disease, were taking medication that would confound the study, had a history of endometrial hyperplasia, or were found to have hyperplasia or endometrial thickness greater than 5 mm or more at baseline. Subjects were randomly assigned to receive bazedoxifene doses ranging from 2.5 mg to 40 mg or to placebo. A total of 497 subjects were available for the endometrial analysis. Compared to placebo, patients who received bazedoxifene 2.5 mg to 20 mg daily did not have a difference in endometrial thickness at days 84 and 168 and those who were randomly assigned to bazedoxifene 30 mg or 40 mg had a significantly smaller change in endometrial thickness from baseline at day 168 (P<.05). Investigators reported a significant inverse relationship between bazedoxifene dose and endometrial thickness found in this trial.

**Phase 3 trials.** Two phase 3 trials have been completed to evaluate the efficacy of bazedoxifene in the treatment and prevention of osteoporosis in postmenopausal women.

The trial by Miller et al was a 2-year, multicenter, double-blind, randomized trial to evaluate the efficacy and safety of bazedoxifene in the prevention of bone loss in generally healthy postmenopausal women. Patients were randomly assigned into 5 groups: bazedoxifene 10 mg, 20 mg, 40 mg, raloxifene 60 mg, and placebo. All subjects also received 600 mg of elemental calcium (calcium carbonate). Women aged ≥45 years who were at least 1 year postmenopause (ie, completed last natural menstrual cycle or underwent bilateral oophorectomy, with or without hysterectomy, at least 1 year before screening) were considered. Additional inclusion criteria were applied based on the years since menopause (Table 1, page 165). The primary efficacy outcome was the change in lumbar spine BMD from baseline after 24 months of therapy. Additional outcomes were the change in BMD from baseline in the total hip, femoral neck, and femoral trochanter;

Continued on page 165
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Important Safety Information

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients.

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

- VIIBRYD (vilazodone) is indicated for the treatment of major depressive disorder (MDD) in adults. The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD.

Important Safety Information (continued)

Contraindications

- VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. Allow at least 14 days after stopping VIIBRYD before starting an MAOI.

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients daily. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

- The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms while treated with VIIBRYD.

- Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

- The use of drugs that interfere with serotonin reuptake, including VIIBRYD, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation or bleeding.

- Symptoms of mania/hypomania were noted in 0.1% of patients treated with VIIBRYD in clinical studies. As with all antidepressants, VIIBRYD should be used cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

- Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. VIIBRYD is not approved for use in treating bipolar depression.

- Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate.

- Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD. Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Adverse Reactions

- The most commonly observed adverse reactions in MDD patients treated with VIIBRYD in placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were: diarrhea (28% vs 9%), nausea (23% vs 5%), insomnia (6% vs 2%), and vomiting (5% vs 1%).

Please also see Brief Summary of Prescribing Information on the following pages and full Prescribing Information at www.viibryd.com.
VIIBRYD (vilazodone HCl)

Takeda

Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidality and thinking about suicide, primarily in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of an antidepressant for a child or adolescent must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in children and adolescents with depression. However, antidepressants are used in a context of treating depression and other severe conditions (for which safer drugs cannot be used) that are themselves associated with a high and immediate risk of suicidal thoughts and actions. Therefore, antidepressants are prescribed in such a context; see prescribing information for each drug for complete warnings, precautions, and contraindications.

Indications and Usage: VIIBRYD is indicated for the treatment of major depressive disorder (MDD). Treatment should be initiated with a dose of 20 mg daily in adults with a diagnosis of MDD [see Clinical Studies]. Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day) depressed mood that usually interferes with daily functioning, and indicates at least 5 of the following 9 symptoms: depressed mood, listlessness in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, thoughts of death or suicide [see Drug Interactions].

Contraindications: Monamine Oxidase Inhibitors - VIIBRYD must not be used concomitantly in patients taking MAOs or in patients who have taken MAOs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with the development of serious, sometimes fatal, hyponatremia, hyperpyrexia, seizures, and death. These effects may be accompanied by confusion, altered mental status, or extreme agitation with a risk of serious outcome if untreated.

Warnings and Precautions: Clinical Worsening and Suicide Risk - Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation or behavior (suicidal thoughts or actions) during the course of treatment with antidepressants. In all randomized, controlled short-term studies of antidepressant drugs in children and adolescents with MDD (aged 8-12 years) and other psychiatric disorders, there were more reports of worsening of depression and suicidality (primarily suicidal ideation and behavior) in the drug treatment groups than in the placebo groups.

Seizures - VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder. Abnormal Bleeding - The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, heparin, and other anticoagulants may have additive effects on platelet inhibition. Patients taking these drugs may have an increased risk of bleeding. Patients with history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for bleeding. Patients with a history of bleeding or patients taking warfarin have been reported in clinical trials. VIIBRYD patients should be monitored for blea...
Laboratory Tests - VIBRYD has been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analyses of (1) mean change from baseline in clinical chemistry tests, (2) differences in blood pressure and heart rate, and (3) changes in body temperature and heart rhythm, among other parameters. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies. ECG - VIBRYD has not been associated with any clinically significant change from baseline in ECG parameters. No patients treated with VIBRYD were withdrawn from the study due to ECG changes (see Clinical Pharmacology). Vital Signs - VIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate in placebo-controlled studies. These studies included analyses of (1) changes from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Adverse Reactions Observed in Clinical Studies - The following listing does not include reactions:

1. already listed in previous tables or elsewhere in labeling;
2. for which a drug cause was remote;
3. which were so generalized as to be a normal clinical finding;
4. which were not considered to have significant clinical implications; or
5. which occurred at a rate equal to or less than placebo.
Reactions are categorized by body system according to the following definitions:

Incidence: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in less than 1/100 patients.

Vascular: abnormal bleeding, bruising, ecchymosis, subcutaneous hemorrhage, epistaxis, hemorrhage, purpura, and petechiae.

Cardiovascular: abnormal heart rate, peripheral edema, palpitations, palpitation, palpitation, and palpitation.

Respiratory: cough, dyspnea, and hyperventilation.

Gastrointestinal: nausea, anorexia, abdominal pain, diarrhea, and vomiting.

Skin and Appendages: rash, pruritus, urticaria, and alopecia.

Neurological: dizziness, headache, and paresthesia.

Psychiatric: irritability, anxiety, and agitation.

Other: infections (upper respiratory tract, ear, nose, and throat), infections (oral cavity, gastrointestinal tract, and skin), and infections (other).

Drug Interactions:

CNS-Active Agents: VIBRYD is generally well tolerated. No drug withdrawal or serious adverse drug reaction was observed in patients treated with VIBRYD who were also treated with other CNS-active agents (e.g., hypnotics, narcotics, or antihypertensives). However, since VIBRYD has been shown to decrease REM sleep and increase SWS, it may potentiate the effects of other CNS-active agents that increase REM sleep and decrease SWS.

Alcohol: No information is available regarding the interaction between VIBRYD and alcohol.

Oversed Management - VIBRYD is not known to cause any drug interactions or adverse reactions when used alone or in combination with other drugs.

Renal Impairment: No information is available regarding the use of VIBRYD in patients with renal impairment.

Dosage Adjustment: No dosage adjustment is necessary based on the information available.

Inhibitors of CYP3A4: VIBRYD is metabolized by CYP3A4, which is a major elimination pathway for vilaconizine. The use of inhibitors of CYP3A4, such as ketoconazole, may increase vilaconizine plasma concentrations by approximately 50% (see Figure 1). The VIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIBRYD dose should be reduced to 10 mg for patients with intravenous adverse events. The use of inhibitors of CYP3A4, such as ketoconazole, may increase the risk of adverse events associated with the use of vilaconizine.

Inducers of CYP3A4: No information is available regarding the use of inducers of CYP3A4 in combination with VIBRYD.

OVERDOSAGE: Human Experience - There is limited clinical experience regarding human overdose with VIBRYD. Four patients and 1 patient's child experienced an overdose of VIBRYD; all recovered. The adverse reactions associated with overdose of VIBRYD at doses of 300-350 mg observed in the clinical trials included symptoms such as dizziness, confusion, drowsiness, nausea, vomiting, headache, and agitation.

Management of Overdose - Consult a Poison Control Center for further guidance and treatment details. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference. In addition, specific antiparkinsonian agents and reversible agonists (e.g., levodopa and carbidopa) are available to treat the symptoms of overdose. In cases of severe toxicity, supportive care, including close medical supervision and monitoring, is recommended.

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## Table 1

### Inclusion and exclusion criteria for phase 3 trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Inclusion</th>
<th>Exclusion</th>
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<tr>
<td>Miller et al, 2008</td>
<td>Women 1-5 years post menopause and at least 1 of the following: lumbar spine or femoral neck BMD T-scores between -1.0 and -2.5 as measured by DXA, family history of fractures, bilateral oophorectomy, current history of smoking, small-boned and/or thin frame (weight &lt;58 kg), inadequate intake of calcium, and little or no weight-bearing exercise. Furthermore, women &gt;5 years post menopause who previously received hormone replacement therapy or had discontinued therapy for ≥6 months or women surgically postmenopausal for &lt;5 years were required to have accompanying serum FSH levels ≥40 IU/L and estradiol levels ≤20 pg/mL.</td>
<td>Other forms of bone disease, conditions that could invalidate BMD testing, at least 1 osteoporotic vertebral fracture shown on thoracolumbar radiographs, history of or active nontraumatic venous thromboembolic event, endometrial hyperplasia based on biopsy or endometrial thickness of ≥5 mm on transvaginal ultrasound, abnormal vaginal bleeding, history of malignancy within previous 10 years, abnormal laboratory tests including abnormal liver function tests or elevated fasting total cholesterol or triglyceride levels (≥310 or ≥300 mg/dL, respectively), and abnormal physical findings including BMI &gt;32.2 kg/m² or elevations in blood pressure, received treatment with any of the following medications: bisphosphonate within 2 years of screening, PTH, a SERM, or an estrogen-, androgen-, or progesterone-containing medication within 6 months of screening, calcitonin or systemic fluoride for &gt;1 month within 6 months of screening, systemic corticosteroid (equivalent to ≥10 mg of prednisone for &gt;10 days) within 6 months of screening, and any investigational drug within 60 days of randomization.</td>
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<tr>
<td>Silverman et al, 2008</td>
<td>Women aged 55 to 85 years at least 2 years post menopause and diagnosed with osteoporosis (low BMD or radiographically confirmed vertebral fractures). Subjects without prevalent vertebral fractures were required to have lumbar spine or femoral neck BMD T-scores between -2.5 and -4.0 (inclusive), whereas subjects with prevalent vertebral fractures (at least 1 mild vertebral fracture) were required to have lumbar spine and femoral neck BMD T-scores not worse than -4.0.</td>
<td>Presence of disease that could affect bone metabolism, conditions that could interfere with bone mineral densitometry, pathologic vertebral fractures, vasomotor symptoms requiring treatment, or serious conditions such as endometrial hyperplasia or carcinoma, abnormal vaginal bleeding, malignancy within 10 years of study, endocrine disorders requiring treatment, or untreated malabsorptive disorders, active or history of DVT or PE or retinal vein thrombosis, elevated fasting total cholesterol or triglycerides (≥310 or ≥300 mg/dL, respectively), use of androgens, systemic estrogens (except estriol ≤2.0 mg/d), topical estrogen (&gt;3 times/wk), progestogens, SERMs, bisphosphonates, calcitonin, PTH, and cholecalciferol (&gt;50,000 IU/wk) within 6 months of screening.</td>
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Abbreviations: BMD, bone mineral density; BMI, body mass index; DVT, deep vein thrombosis; DXA, dual-energy X-ray absorptiometry; FSH, follicle-stimulating hormone; PE, pulmonary embolism; PTH, parathyroid hormone; SERM, selective estrogen receptor modulator

Formulary/Source: Refs 17, 18

Continued on page 170
AXIRON® is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from conditions such as tumors, trauma, or radiation. These men have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

Important limitations of use: safety and efficacy of AXIRON in males <18 years old have not been established.

Select Important Safety Information

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE
• Virilization has been reported in children who were secondarily exposed to topical testosterone products.
• Children should avoid contact with unwashed or unclad application sites in men using AXIRON.
• Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

For men with low or no testosterone, AXIRON:

• Is the first and only topical testosterone solution applied via an underarm applicator
• Restored testosterone levels to normal range in most men
  ~84% of men who had sufficient data for analysis (n=138) finished the study with average testosterone levels in the normal range
  ~75% of responding patients (n=138) finished the study on the recommended 60-mg starting dose
• Most common adverse reactions included application site irritation (7%), application site erythema (5%), headache (5%), increased hematocrit (4%), diarrhea (3%), vomiting (3%), and increased PSA (1%)

See additional Important Safety Information on the adjacent page and Brief Summary of Prescribing Information on the following pages.
Important Safety Information for AXIRON

CONTRAINDICATIONS

AXIRON is contraindicated in:

- men with carcinoma of the breast or known or suspected carcinoma of the prostate
- women who are, or who may become pregnant, or who are breastfeeding. AXIRON may cause fetal harm when administered to a pregnant woman. AXIRON may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to AXIRON, she should be apprised of the potential hazard to the fetus

WARRANTS and PRECAUTIONS:

- Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer: Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. Patients treated with Androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It would be appropriate to re-evaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices.
- Potential for Secondary Exposure to Testosterone: Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen or upper arms, including cases of secondary exposure resulting in virilization of children. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AXIRON. Inappropiate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician. The possibility of secondary exposure to testosterone should also be brought to the attention of a physician. Testosterone therapy should be promptly discontinued at least until the cause of virilization has been identified.
- Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AXIRON treated skin:
  - Children and women should avoid contact with the unclothed or unwashed application sites on the skin of men using AXIRON.
  - Patients should wash their hands immediately with soap and water after application of AXIRON.
  - Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the solution has dried.
  - Prior to any situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
  - In the event that unwashed or unclothed skin to which AXIRON has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.
  - While interpersonal testosterone transfer can occur with a T-shirt on, it has been shown that transfer can be substantially reduced by wearing a T-shirt and the majority of residual testosterone is removed from the skin surface by washing with soap and water.

For more information, please see the Brief Summary of full Prescribing Information on the following pages or visit www.axiron.com.

- Polycythemia: Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.
- Potential for Adverse Effects on Spermatogenesis: At large doses of exogenous androgens, including AXIRON, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.
- Edema: Androgens, including AXIRON, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease.
- Gynecomastia: Gynecomastia may develop and may persist in patients being treated with androgens, including AXIRON, for hypogonadism.
- Sleep Apnea: The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity and chronic lung disease.
- Lipids: Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.
- Hypercalcemia: Androgens, including AXIRON, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.
- Decreased Thyroxine-binding Globulin: Androgens, including AXIRON, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentration and increased resin uptake of T3 and T4. Free thyroid hormone concentration remain unchanged, however there is no clinical evidence of thyroid dysfunction.
- Flammability: Patients should be advised to avoid smoking, fire, or flame until the AXIRON dose applied has dried.

DRUG INTERACTIONS:

- Insulin: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.
- Oral anti-coagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.
- Corticosteroids: Concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal, or hepatic disease.

USE IN SPECIFIC POPULATIONS:

- Geriatric Use: There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AXIRON to determine whether efficacy in those over 65 years of age differs from younger patients. Of the 155 patients enrolled in the pivotal clinical study utilizing AXIRON, 21 were over 65 years of age. Additionally, there were insufficient long-term safety data in these patients utilizing AXIRON to assess a potential incremental risk of cardiovascular disease and prostate cancer.

ADVERSE REACTIONS:

- Most common adverse reactions included application site irritation (7%), application site erythema (5%), headache (5%), increased hematocrit (4%), diarrhea (3%), vomiting (3%), and increased PSA (1%).
AXIRON® (testosterone) topical solution CIII

**Brief Summary:** The following is a brief summary of the full prescribing information for AXIRON® (testosterone) solution. Please review the full prescribing information prior to prescribing AXIRON®.

**WARNING: SECONDARY EXPOSURE TO TESTOSTERONE**
- Virilization has been reported in children who were secondarily exposed to topical testosterone products
- Children should avoid contact with unwashed or unclothed application sites in men using AXIRON
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use

**INDICATIONS AND USAGE**
AXIRON is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Important limitations of use – Safety and efficacy of AXIRON in males <18 years old have not been established.

**CONTRAINDICATIONS**
AXIRON should not be used in:
- men with carcinoma of the breast or known or suspected carcinoma of the prostate.
- women who are, or who may become pregnant, or who are breastfeeding. AXIRON may cause fetal harm when administered to a pregnant woman. AXIRON may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to AXIRON, she should be apprised of the potential hazard to the fetus.

**WARNINGS AND PRECAUTIONS**

Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer: Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. Patients treated with Androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It would be appropriate to reevaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices.

Potential for Secondary Exposure to Testosterone
Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen or upper arms, including cases of secondary exposure resulting in virilization of children. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AXIRON.

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone should also be brought to the attention of a physician. Testosterone therapy should be promptly discontinued at least until the cause of virilization has been identified.

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from AXIRON treated skin:
- Children and women should avoid contact with the unclothed or unwashed application sites on the skin of men using AXIRON.
- Patients should wash their hands immediately with soap and water after application of AXIRON.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the solution has dried.
- Prior to any situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AXIRON has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.
- While interpersonal testosterone transfer can occur with a T-shirt on, it has been shown that transfer can be substantially reduced by wearing a T-shirt and the majority of residual testosterone is removed from the skin surface by washing with soap and water.

Polycythemia: Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

Use in Women: AXIRON is not indicated for use in women.

Potential for Adverse Effects on Spermatogenesis: At large doses of exogenous androgens, including AXIRON, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

Hepatic Adverse Effects: Prolonged use of high doses of orally active 17-alpha-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects (pelasis hepatitis, hepatic neoplasms, cholestasis, hepatic, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AXIRON is not known to cause these adverse effects.

Edema: Androgens, including AXIRON, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease.

Gynecomastia: Gynecomastia may develop and may persist in patients being treated with androgens, including AXIRON, for hypogonadism.

Sleep Apnea: The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity and chronic lung disease.

Lipids: Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.
Hypercaldemia: Androgens, including AXIRON, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

Decreased Thyroxine-binding Globulin: Androgens, including AXIRON, may decrease levels of thyroxine-binding globulins, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged; however, there is no clinical evidence of thyroid dysfunction

Famibility: Patients should be advised to avoid smoking, fire, or flame until the AXIRON dose applied has dried.

ADVERSE REACTIONS

Clinical Trial 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.

Clinical Trials in Hypogonadal Men: Table 1 shows the treatment emergent adverse reactions that were reported by either >4% of 155 patients in a 120 day, Phase 3 study or by >4% of 71 patients who continued to use AXIRON for up to 180 days. These data reflect the experience primarily with a testosterone dose of 60 mg, which was taken by all patients at the start of the study, and was the maintenance dose for 97 patients. However, the doses used varied from 30 mg to 120 mg.

### Table 1: Adverse Reactions Seen With the Use of AXIRON in either the 120 Day Clinical Trial or in the Extension to 180 Days (>4%)

<table>
<thead>
<tr>
<th>Event</th>
<th>120 Days (155 Patients)</th>
<th>180 Days (71 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Irritation</td>
<td>11 (7%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Application Site Erythema</td>
<td>8 (5%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (5%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Hematocrit Increased</td>
<td>6 (4%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>PSA Increased</td>
<td>2 (1%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Other less common adverse reactions reported by at least 2 patients in the 120 day trial included: application site edema, application site warmth, increased hemoglobin, increased blood pressure, increased blood testosterone, increased blood glucose, acne, nasopharyngitis, anger and anxiety. Other less common adverse reactions reported in fewer than 1% of patients in the 120 day trial included: asthenia, affect lability, erythema (general), folliculitis, anxiety, increased lacrimation, breast tenderness, hypertension, neoplasm prostate and elevated red blood cell count.

During the 120 day trial one patient discontinued treatment because of affect lability/anger which was considered possibly related to AXIRON administration.

During the 120 day clinical trial there was an increase in mean PSA values of 0.13 ± 0.68 ng/dL from baseline. At the end of the 180 day extension clinical trial, there was an overall increase in mean PSA values of 0.1 ± 0.54 ng/dL. Neither change was statistically significant.

Following the 120 day study, seventy-one (71) patients entered a two-month extension study with AXIRON. Two patients (3%) had adverse reactions that led to discontinuation of treatment during the period from Day 120 to Day 180. These reactions were: one patient with application site irritation (considered possibly related to AXIRON application) and one patient with dry skin and erythema, but not at the application site (considered not related to AXIRON administration) and application site erythema (considered possibly related to AXIRON administration). No serious adverse reactions to AXIRON were reported during either the 120 day trial, or the extension to 180 days.

### Drug Interactions

**Insulin:** Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.

**Oral anti-coagulants:** Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

**Corticosteroids:** The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

### Use in Specific Populations

**Pregnancy Category X:** AXIRON is not indicated for use in pregnant or breastfeeding women and must not be used in women. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**Nursing Mothers:** Although it is not known how much testosterone transfers into human milk, AXIRON is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation.

**Pediatric Use:** Safety and efficacy of AXIRON has not been established in males <18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

**Geriatric Use:** There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AXIRON to determine whether efficacy in those over 65 years of age differs from younger patients. Of the 155 patients enrolled in the pivotal clinical study utilizing AXIRON, 21 were over 65 years of age. Additionally, there were insufficient long-term safety data in these patients utilizing AXIRON to assess a potential incremental risk of cardiovascular disease and prostate cancer.

**Renal or Hepatic Impairment:** No formal studies were conducted involving patients with renal or hepatic insufficiencies.

### Drug Abuse and Dependence

**Controlled Substance:** AXIRON contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. Oral ingestion of AXIRON is not expected to result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

**Overdose:** No cases of overdose with AXIRON have been reported in clinical trials. There is one report of acute overdose by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdose would consist of discontinuation of AXIRON together with appropriate symptomatic and supportive care.

**Storage and Handling - Keep AXIRON out of reach of children.** Store at 25°C (77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Used in a manner that prevents accidental exposure of children or pets.

Additional information can be found at www.Axiron.com.

**TS Hypogonadism HCP BS: (22_FEB_2011), PV 8150**
change in CTX and serum osteocalcin at 12 months; and changes in the lipid profile. All efficacy outcomes were analyzed in subjects who were randomly assigned, received at least 1 dose of study drug, had at least 1 screening assessment, and had at least 1 BMD assessment on therapy.\textsuperscript{17}

A total of 1,583 women from 101 centers in Canada, the United States, and Europe were randomly assigned and received at least 1 dose of bazedoxifene 10 mg (n=321), 20 mg (n=322), 40 mg (n=319), raloxifene 60 mg (n=311), or placebo (n=310).\textsuperscript{17} The mean age of enrolled subjects was 58 years and the majority of subjects were white (94%). The average number of years since last menstrual period ranged from 10.46 to 11.25 and the mean reported BMD in the treatment groups was no lower than -1.24 at any of the measured locations (lumbar spine, total hip, femoral neck, or femoral trochanter). A total of 1,113 subjects completed the trial (70.3%). A total of 470 participants (29.6%) withdrew from the trial with the most common reason being adverse events (54.9% of withdrawals). A similar percentage of participants withdrew from the trial due to any adverse event across the 5 groups (bazedoxifene 10 mg 16.8%, 20 mg 17.1%, 40 mg 18.2%, raloxifene 60 mg 13.8%, placebo 15.5%).\textsuperscript{17}

Of the overall number of women randomly assigned, 1,434 were evaluable for BMD analysis of the lumbar spine and 1,430 were evaluable for BMD analysis of the total hip, femoral neck, and femoral trochanter (Table 2, page 171-172).\textsuperscript{17} The primary efficacy outcome, BMD at the lumbar spine at 24 months, was significantly greater in each of the bazedoxifene groups versus placebo (Table 2).\textsuperscript{17} The BMD at the lumbar spine significantly increased from baseline in patients who received bazedoxifene 40 mg (P<.001) but was not significantly different for those who received 10 mg or 20 mg and was significantly decreased in the placebo group (P<.001). All treatment groups had significantly greater BMD of the total hip versus placebo (Table 2).\textsuperscript{17} Authors reported that all active treatment groups had preserved BMD of the total hip, whereas those in the placebo group had a significant decrease from baseline (P<.001). The changes in BMD of the lumbar spine and total hip in patients who received bazedoxifene were similar to those who received raloxifene at 6 months and throughout the study period. Similar findings were reported for the BMD of the femoral neck and femoral trochanter, with bazedoxifene 20-mg and 40-mg groups demonstrating significantly increased BMD versus placebo. The BMD of the femoral neck was significantly greater in the bazedoxifene 20-mg and 40-mg groups versus the 10-mg group and were reported to be equally as effective as raloxifene in improving femoral neck BMD, whereas all 3 doses were comparable to raloxifene in the effect on BMD of femoral trochanter. Patients in the bazedoxifene and raloxifene groups had significantly lower levels of serum osteocalcin and CTX versus placebo or compared to baseline as well as neutral to favorable effects on the lipid profile (Table 2).\textsuperscript{17}

The trial by Silverman et al was a 3-year, multicenter, double-blind randomized trial comparing once-daily doses of bazedoxifene 20 mg or 40 mg to raloxifene 60 mg or placebo.\textsuperscript{18} All subjects also received up to 1,200 mg of calcium and 400 to 800 IU of vitamin D orally daily. Women between aged 55 and 85 years and at least 2 years post menopause with osteoporosis, defined as low BMD or radiographically confirmed vertebral fractures, were considered for inclusion with additional criteria applied (Table 1, page 165).\textsuperscript{18} The primary efficacy outcome was the incidence of new vertebral fractures after 36 months of therapy. Secondary outcomes included the incidence of clinical vertebral fractures and nonvertebral fractures, change in the BMD from baseline in the lumbar spine, total hip, or femoral neck, and serum osteocalcin and CTX levels. Analysis of the primary outcome was in subjects who were randomly assigned, received at least 1 dose of study drug, and underwent vertebral radiography at baseline and at least once during therapy.\textsuperscript{18}

A total of 7,492 subjects were randomly assigned to and received at least 1 dose of bazedoxifene 20 mg (n=1,886), 40 mg (n=1,872), raloxifene 60 mg (n=1,849), or placebo (n=1,885).\textsuperscript{18} The mean age of enrolled subjects was 66 years and the majority of subjects were of white ethnic origin (87%). The mean number of years since last menstrual period ranged from 19.3 to 19.7. Mean baseline lumbar spine T-scores were -2.4 in all groups and the mean femoral neck T-score ranged from -1.7 to -1.8. A total of 4,991 subjects completed the study (66.6%) with adverse events leading to the most discontinuations (bazedoxifene 20 mg 42.6%, 40 mg 42.0%, raloxifene 60 mg 43.9%, placebo 38.2%).\textsuperscript{18} A significantly higher percentage of subjects who discontinued therapy due to a new vertebral fracture or loss of BMD ≥7% was found in the placebo group compared to the active treatment groups.\textsuperscript{18}

Among the 6,847 subjects making up the intent-to-treat population, all treatment groups had a significantly lower incidence of a new vertebral fracture after 36 months of treatment versus placebo and there was no significant difference between the groups (Table 2).\textsuperscript{18} There was no significant difference in the incidence of nonvertebral fractures among the treatment groups. A post-hoc analysis evaluated a subgroup of women (n=1,772) at higher baseline risk of fractures and found that bazedoxifene 20 mg significantly reduced the risk of nonvertebral fractures compared to placebo (hazard ratio [HR], 0.50; CI, 0.28-0.90); although this was not significantly different versus raloxifene or when bazedoxifene 40 mg was compared to placebo or raloxifene. In the subgroup considered to be at lower risk, no significant differences were found in the incidence of nonvertebral fractures between the groups.\textsuperscript{18}
# Table 2

**Outcomes from phase 3 trials (and post-hoc analyses) evaluating bazedoxifene for treatment and prevention of osteoporosis**

<table>
<thead>
<tr>
<th>Author, Year (n)</th>
<th>Arm</th>
<th>Incidence of new vertebral fractures</th>
<th>Incidence of nonvertebral fractures</th>
<th>Mean % change in lumbar BMD</th>
<th>Mean % change in total hip BMD</th>
<th>Change in CTX</th>
<th>Change in serum osteocalcin level</th>
<th>Median % change in lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al, 2008* (n=1,434; n=1,430)</td>
<td>BZD 10 mg</td>
<td>Not evaluated in this trial</td>
<td>Not evaluated in this trial</td>
<td>1.08±0.28*</td>
<td>1.29±0.21*</td>
<td>-25%*</td>
<td>-21%*</td>
<td>TC: -2.86 (-8.47 to 6.89) * LDL-C: -2.97 (-14.69 to 10.43) * HDL-C: 1.08 (-9.57 to 10.38) * TG: 0.00 (-22.09 to 27.06)</td>
</tr>
<tr>
<td></td>
<td>BZD 20 mg</td>
<td>1.41±0.28*</td>
<td>1.75±0.21*</td>
<td>-24%*</td>
<td>-22%*</td>
<td>TC: -0.32 (-9.42 to 5.59) LDL-C: -5.76 (-14.81 to 6.17) HDL-C: 0.00 (-8.65 to 7.51) TG: 12.26 (-16.95 to 37.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BZD 40 mg</td>
<td>1.49±0.28*</td>
<td>1.60±0.21*</td>
<td>-22%*</td>
<td>-22%*</td>
<td>TC: -4.23 (-11.02 to 3.38) LDL-C: -9.66 (-17.81 to 1.70) HDL-C: -3.40 (-13.33 to 7.81) TG: 12.94 (-12.24 to 41.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene 60 mg</td>
<td>NR</td>
<td>NR</td>
<td>-32%</td>
<td>-27%</td>
<td>TC: -6.27 (-13.26 to 3.93) LDL-C: -11.82 (-20.83 to 0.79) HDL-C: -2.89 (-12.68 to 10.67) TG: 0.94 (-26.09 to 30.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
<td>-13%</td>
<td>-6%</td>
<td>TC: 1.46 (-6.10 to 9.66) LDL-C: 2.63 (-8.33 to 14.57) HDL-C: 2.94 (-12.94 to 5.83) TG: 4.70 (-18.70 to 33.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silverman et al, 2008** (n=6,847)</td>
<td>BZD 20 mg</td>
<td>2.3% HR 0.58 (CI, 0.38 to 0.89)</td>
<td>5.7%</td>
<td>2.21±0.16*</td>
<td>0.27±0.12*</td>
<td>-46%</td>
<td>-37%</td>
<td>TC: -3.8 (NR) * LDL-C: -5.4 (NR) * HDL-C: 5.1 (NR) * TG: 8.5 (NR)</td>
</tr>
<tr>
<td></td>
<td>BZD 40 mg</td>
<td>2.5% HR 0.63 (CI, 0.42 to 0.96)</td>
<td>5.6%</td>
<td>2.38±0.16*</td>
<td>0.50±0.12*</td>
<td>-49%</td>
<td>-39%</td>
<td>TC: -3.5 (NR) * LDL-C: -6.6 (NR) * HDL-C: 5.9 (NR) * TG: 13.6 (NR)</td>
</tr>
<tr>
<td>Raloxifene 60 mg</td>
<td>2.3% HR 0.58 (CI, 0.38 to 0.89)</td>
<td>5.9%</td>
<td>2.96±0.16*</td>
<td>0.90±0.12*</td>
<td>-55%</td>
<td>-41%</td>
<td>TC: -5.0 (NR) * LDL-C: -8.5 (NR) * HDL-C: 5.0 (NR) * TG: 12.2 (NR)</td>
<td></td>
</tr>
</tbody>
</table>

Continued on Page 172
**Focus on bazedoxifene**

An independent post-hoc re-analysis of the core trial evaluated the risk of vertebral and all clinical fractures in the bazedoxifene 20-mg and 40-mg groups combined versus placebo using multivariate analysis. Baseline fracture risk was assessed using the computer-based FRAX algorithms and the 10-year probability of having a new fracture was estimated. Bazedoxifene did not significantly reduce the risk of all clinical fractures (HR, 0.84; CI, 0.67–1.06); however, as the baseline risk for fractures increased, the HR continued to decrease until the baseline risk of 16%, which was the threshold for probability at which treatment had a significant effect. The BMD of the lumbar spine and of the total hip were significantly greater in both bazedoxifene groups versus placebo at 36 months in the core trial (Table 2). Authors also reported a small but significant difference at each time point between both bazedoxifene doses and raloxifene throughout the study period for both BMD of the lumbar spine (P<.05) and total hip (P<.01). Compared to placebo, patients in the bazedoxifene and raloxifene groups had significantly decreased serum osteocalcin and CTX levels (Table 2). The difference between the bazedoxifene and raloxifene groups of both markers was statistically significant (P<.001). Similar to the trial by Miller et al, bazedoxifene had a neutral to favorable effect on the lipid profile (Table 2). A 2-year extension of the core trial enrolled 4,216 subjects (Table 2). The raloxifene arm was discontinued and subjects originally randomly assigned to bazedoxifene 40 mg were blindly transitioned to 20 mg (bazedoxifene 40/20 mg). Similar to the core trial, there was a significant reduction in the risk of new vertebral fractures in the bazedoxifene 20 mg and 40/20 mg groups versus placebo at 5 years and no significant difference in the risk of nonvertebral fractures between groups in the overall population (Table 2). In a subgroup of high-risk patients, a

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**Table 2 continued from Page 171**

<table>
<thead>
<tr>
<th>Author, Year (n)</th>
<th>Arm</th>
<th>Incidence of new vertebral fractures</th>
<th>Incidence of nonvertebral fractures</th>
<th>Mean % change in lumbar BMD</th>
<th>Mean % change in total hip BMD</th>
<th>Change in CTX</th>
<th>Change in serum osteocalcin level</th>
<th>Median % change in lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4.1%</td>
<td>6.3%</td>
<td>0.88±0.16</td>
<td>-0.83±0.12</td>
<td>-27%</td>
<td>-21%</td>
<td>TC: 0.3 (NR)‡‡</td>
<td>LDL-C: 1.6 (NR)‡‡, HDL-C: 2.5 (NR)‡‡, TG: 12.1 (NR)‡‡</td>
</tr>
<tr>
<td>Silverman et al, 2009 (n=4,216)</td>
<td>BZD 20 mg</td>
<td>4.5%††</td>
<td>9.5%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>BZD 40/20 mg</td>
<td>3.9%††</td>
<td>7.6%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.8%</td>
<td>9.0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Levine et al, 2009 (n=505)</td>
<td>BZD 20 mg</td>
<td>1.7%</td>
<td>NR</td>
<td>0.88±0.64§</td>
<td>1.24±0.53§</td>
<td>-47%§</td>
<td>-42%†</td>
<td>NR</td>
</tr>
<tr>
<td>BZD 40 mg</td>
<td>2.1%</td>
<td>NR</td>
<td>1.14±0.60§</td>
<td>1.18±0.49§</td>
<td>-57%§</td>
<td>-44%†</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>0.8%</td>
<td>NR</td>
<td>1.42±0.63§</td>
<td>1.06±0.51§</td>
<td>-57%§</td>
<td>-45%†</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.6%</td>
<td>NR</td>
<td>-0.25±0.62</td>
<td>-0.06±0.51§</td>
<td>-35%</td>
<td>-24%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Number based on the intention-to-treat criteria of trial; 1,434 women were evaluated for the BMD of lumbar spine and 1,430 were evaluated for the total hip, femoral neck, and femoral trochanter BMD. Outcomes evaluated at 24 months. BMD reported as mean (± standard deviation).†P<.001 ††P<.001 versus placebo ‡P<.05 versus placebo ‡‡Outcomes evaluated at 36 months. Reported HR ratios are versus placebo. BMD are reported as mean (± standard error). Lipid data from safety analysis by Christiansen et al, 2010. P=.01 versus placebo for the BZD 20-mg group and P=.005 for the BZD 40/20-mg group ††P<.001 versus baseline ‡‡P<.01 versus raloxifene

**Abbreviations:** BMD, bone mineral density; BZD, bazedoxifene; CI, confidence interval; CTX, serum type 1 collagen C-telopeptide; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; m, months; NR, not reported; TC, total cholesterol; TG, triglycerides

Formulary/Source: Refs 17,18,23,24
As a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

**Indications and Usage**
DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**
DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

**Warnings and Precautions**
- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.
- Prescribers should monitor weight regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended.

**Adverse Reactions**
In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see Brief Summary of full Prescribing Information on the following page.
DALIRESP® (roflumilast) tablets  Rx Only
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2011

INDICATIONS AND USAGE
DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use
DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS
The use of DALIRESP is contraindicated in the following conditions: 
- Moderate or severe liver impairment (see Warnings and Precautions [5.4]).
- Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. 
- Treatment of Acute Bronchospasm
DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events Including Suicidality
Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions, in 8 controlled clinical trials 5.9% (281) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [see Adverse Reactions (6.1)]. Incidences of suicidal ideation and behavior including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) receiving placebo. 

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and consider the risk-benefit of administering DALIRESP to patients who wish to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease
Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see Adverse Reactions (6.1)]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients receiving placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During long-term discontinuation, the population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean prebronchodilator forced expiratory volume in one second (FEV1) of 8.9% to 89.1% predicted. In these trials, 65.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 8.8% in the roflumilast-treated patient and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%). Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostatic cancer, acute pancreatitis, and acute renal failure. Table 1 summarizes the adverse reactions in greater than or equal to 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo Rate

Dizziness    92 (2.1) 45 (1.1)
Drowsiness    89 (1.9) 31 (0.8)
Headache    195 (4.4) 113 (2.7)
ITCHY SKIN    111 (2.4) 60 (1.5)
Joint pain    59 (1.3) 31 (0.8)
Joint swelling    74 (1.6) 34 (0.8)
Nausea    100 (2.1) 18 (0.4)
Sweating    51 (1.1) 11 (0.3)
Nasal congestion    65 (1.4) 44 (1.1)
UlceraPostNatal    70 (1.5) 18 (0.4)

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/m2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forlinmbo grip reflex and delayed pinna detatchment in newborn mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m2 basis at a maternal dose of ≥ 2 mg/kg/day).

Labor and Delivery
DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP-induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m2 basis at a maternal dose of ≥ 2 mg/kg/day).

Nursing Mothers
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use
COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use
Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were ≥ 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses in the elderly and younger patients. Because elderly patients may have increased sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted [see Clinical Pharmacology (12.3)].

Hepatic Impairment
Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively, in the roflumilast-N-oxide group (on a mg/m2 basis) compared to age-, weight- and gender-matched healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3)].

Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were increased by 20% and 41%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3)].
SAFETY AND TOLERABILITY

A total of 9,075 women comprised the safety population in the phase 3 clinical trials and 5-year data were available for 3,146 women. The most common side effects (reported by ≥20% in at least 1 group in 1 trial) in the core phase 3 trials were headache, infection, arthralgia, pain, hot flashes, back pain, abdominal pain, accidental injury, flu syndrome, and hypertension, and were similar to those reported common at 5 years. A higher percentage of women reported hot flashes in the bazedoxifene groups versus placebo, although this was similar to raloxifene-treated patients. This effect persisted in the 5-year safety data with significantly higher changes in BMD at the lumbar spine, total hip, femoral neck, and femoral trochanter from baseline versus placebo at 24 months (Table 2).

To evaluate bazedoxifene’s effects on endometrial, ovarian, and breast tissues, several safety analyses of the phase 3 trials have been conducted. Endometrial and ovarian safety analyses of 1,116 and 1,387 subjects, respectively, from the trial by Miller et al were conducted. No significant changes were found in endometrial thickness from baseline to 24 months in the bazedoxifene groups. No patients were diagnosed with endometrial hyperplasia and there was no significant difference in the rate of endometrial polyp formation or in reported gynecologic or endometrial adverse events. Authors concluded that safety findings for bazedoxifene and raloxifene in this study were comparable and that bazedoxifene does not seem to stimulate endometrial, ovarian, or breast tissue. Endometrial, ovarian, and breast safety was evaluated in a subset of 753 women from the trial by Silverman et al., the overall incidence of cardiovascular events (coronary occlusion, MI, myocardial ischemia) was not significantly different between groups. Cerebrovascular adverse events including outcomes such as hemorrhagic or ischemic stroke were rare in both trials. The rate of stroke per 1,000 women-years was 2.6, 3.1, 2.6, and 3.0 in bazedoxifene 20 mg, 40 mg, raloxifene 60 mg, and placebo groups, respectively. Venous thromboembolism (VTE) was rare in bazedoxifene-treated patients in the trial by Miller et al (2 deep vein thromboses [DVTs], 1 pulmonary embolism, and 0 retinal vein thrombosis). However, in the trial by Silverman et al, there was a higher incidence of any VTE (primarily DVT) in the bazedoxifene- and raloxifene-treated patients compared to placebo, but no difference compared to each other. The rates of VTE and DVT per 1,000 women-years were: 2.8 and 1.7 in bazedoxifene 20 mg, 2.9 and 2.0 in bazedoxifene 40 mg, 2.0 and 1.5 in raloxifene 60 mg, and 1.7 and 0.2 in placebo, respectively.

Safety parameters of interest in phase 3 trials included cardiovascular and thromboembolic events. In the trial by Miller et al., 3 myocardial infarctions (MIs) occurred in bazedoxifene-treated patients and 1 occurred in a placebo-treated patient. In the trial by Miller et al., myocardial infarction (MI), myocardial ischemia (MI) was not significantly different between groups. Cerebrovascular adverse events including outcomes such as hemorrhagic or ischemic stroke were rare in both trials. The rate of stroke per 1,000 women-years was 2.6, 3.1, 2.6, and 3.0 in bazedoxifene 20 mg, 40 mg, raloxifene 60 mg, and placebo groups, respectively. Venous thromboembolism (VTE) was rare in bazedoxifene-treated patients in the trial by Miller et al (2 deep vein thromboses [DVTs], 1 pulmonary embolism, and 0 retinal vein thrombosis). However, in the trial by Silverman et al, there was a higher incidence of any VTE (primarily DVT) in the bazedoxifene- and raloxifene-treated patients compared to placebo, but no difference compared to each other. The rates of VTE and DVT per 1,000 women-years were: 2.8 and 1.7 in bazedoxifene 20 mg, 2.9 and 2.0 in bazedoxifene 40 mg, 2.0 and 1.5 in raloxifene 60 mg, and 1.7 and 0.2 in placebo, respectively.

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Focus on bazedoxifene

Silverman et al. No significant differences were seen in endometrial thickness, ovarian size, number of ovarian cysts, abnormalities of cervical cytology, breast carcinoma, breast cysts, or breast pain between groups. There was a significant difference in the incidence of ovarian carcinoma between groups (bazedoxifene 20 mg 5 cases, 40 mg 0 cases, raloxifene 2 cases, placebo 0 cases, P<.023), although when classified as treatment-emergent, the difference was no longer significant. The raloxifene group had a significantly higher incidence of fibrocystic breast disease (0.8%) compared to bazedoxifene 20 mg (0.3%) or 40 mg (0.2%, P=.05). A retrospective study of mammography data from a subset of eligible participants (n=444) from the trial by Silverman et al evaluated the change in breast density from baseline to month 24 and found no significant differences between groups. The 5-year safety data were overall consistent with the data available after 3 years. The incidence of breast carcinoma was similar across bazedoxifene and placebo groups and the incidence of breast pain, cysts, or fibrocystic disease was not significantly different. A lower incidence of endometrial carcinoma was observed in bazedoxifene-treated patients (0% and 0.2%) versus placebo (0.3%, P=.05). The mean change in endometrial thickness was not significantly different between bazedoxifene and placebo groups. Four cases of ovarian carcinoma occurred, all in the bazedoxifene groups.

DRUG INTERACTIONS

Bazedoxifene is extensively metabolized via glucuronidation and has little to no cytochrome P450-mediated metabolism; therefore the likelihood of significant drug interactions is low. Bazedoxifene was studied with ibuprofen for clinically relevant PK interactions because both drugs are metabolized via glucuronidation
and may be taken concurrently. An open-label, 3-way crossover study in 12 healthy postmenopausal women with single doses of bazedoxifene 20 mg and ibuprofen 600 mg found no significant alterations in PK parameters. Authors concluded the drugs can be taken together safely without the need for dosage adjustment.

**DOSEING AND ADMINISTRATION**

Although not yet FDA approved, bazedoxifene has been studied for the prevention and treatment of osteoporosis in postmenopausal women with doses ranging from 10 mg to 40 mg daily. It is, however, worth noting that the 10-mg dose was found to be less effective in protecting against bone loss than the 20-mg and 40-mg doses. No data were identified to suggest specific administration of bazedoxifene relative to meals or to suggest dose adjustment in patients with renal or hepatic impairment.

**FORMULARY CONSIDERATIONS**

Bazedoxifene is currently under investigation for the treatment and prevention of osteoporosis in postmenopausal women. In phase 3 trials, bazedoxifene reduced the risk of new vertebral fractures in women with osteoporosis by 37% to 42% compared to placebo, while decreasing the risk of nonvertebral fractures in a post-hoc subgroup analysis of women with higher baseline risk of fractures. Bazedoxifene also led to preservation of BMD in the lumbar spine and areas of the hip compared to placebo. From this data, bazedoxifene appears similar in efficacy to raloxifene in both prevention of fractures and preservation of BMD. Bazedoxifene appears to have a favorable safety profile on lipids, endometrial, ovarian, and breast tissue. Other adverse events such as VTE may occur more frequently than placebo but appear similar to raloxifene, as does the occurrence of hot flushes. Additionally, the dose regimens studied to date are once daily and the propensity for clinically significant drug interactions with bazedoxifene is lower given its primary metabolic pathways.

**REFERENCES**


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A review of systemic lupus erythematosus and current treatment options

Allison Bernknopf, PharmD, BCPS; Kristina Rowley, PharmD, CDE; Teresa Bailey, PharmD, BCPS, FCCP

Systemic lupus erythematosus (SLE) is a multi-organ, autoimmune, inflammatory disease. The annual incidence of SLE in the United States ranges from 2.0 to 7.6 cases per 100,000 persons per year and the prevalence of SLE ranges from 14.6 to 68 cases per 100,000 persons. Five-year survival rates have increased from half of patients to 88% to 96% of patients diagnosed with SLE. Ten-year survival rates are 95% and 71% for younger and older patients, respectively. The 20-year survival rates are now estimated at 80% of patients, due to earlier diagnosis and more effective treatment options.

SLE predominantly affects adults, usually women of childbearing age (20 to 40 years), at a female to male ratio of 9:1 to 15:1. Approximately 8% to 15% of SLE cases occur in children. Older adults diagnosed with SLE, such as postmenopausal women, usually have a milder form. Genetic and racial factors are also associated with an increased risk of developing SLE. African-American women have a 3 to 4 times higher prevalence of SLE than Caucasian women. Additionally, those of Afro-Caribbean, Asian, Native American, and Hispanic descent have a higher incidence of SLE compared to Caucasian individuals. This differs from drug-induced lupus erythematosus (DILE), which occurs at similar rates in men and women but with a higher incidence and severity in Caucasian compared to African-American patients.

PATHOPHYSIOLOGY/ETIOLOGY

The development of SLE is a complex immune process that is brought about by dysregulation of B- and T-lymphocytes, the production of auto-antibodies, and the formation of immune complexes. Cytokines are thought to play a key role in SLE; however, the extent to which they affect progression of lupus is not clear. Their involvement may help explain the variations seen in the clinical manifestations of patients. More research is needed to identify the role of cytokines in order to better understand the disease progression as well as find new treatment options.

While it is known that the immune system plays a role in the development of the disease, what causes the immune system to function abnormally is unknown. It is speculated that environmental factors play a role, but the data have not consistently supported this theory. Use of hormone replacement therapy has also been shown to increase the risk of developing SLE. Estrogen and androgen metabolism have been found to differ in men and women with SLE compared with healthy controls. For example, women with SLE metabolize estrogen to a more potent form, 16a-hydroxyestrone, instead of 2-hydroxyestrone, and can have irregular menstruation cycles and increased risk of miscarriage. Prolactin levels can also be elevated in patients with SLE.

There is also some evidence that hormone abnormalities are associated with SLE. Estrogen and androgen metabolism have been found to differ in men and women with SLE compared with healthy controls. For example, women with SLE metabolize estrogen to a more potent form, 16a-hydroxyestrone, instead of 2-hydroxyestrone, and can have irregular menstruation cycles and increased risk of miscarriage. Prolactin levels can also be elevated in patients with SLE. Use of hormone replacement therapy has also been shown to increase the risk of developing SLE. Infection with the Epstein-Barr virus has been associated with the production of auto-antibodies that are present in up to 38% of patients with SLE. However, it is not clear if these actually lead to the development of SLE or just occur concomitantly.

Lupus may also develop as a result of exposure to various medications. Up to 10% of patients presenting or diagnosed with SLE may actually have DILE, and approximately 80 drugs have been implicated in causing DILE. The vast

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majority of these drugs, however, only have a handful of case reports.\textsuperscript{8–10} Table 1 (page 180) lists common medications known to induce DILE. Some biologic medications have also been implicated in the development of DILE. Ramos-Casals and colleagues found 92 case reports of DILE between 1990 and 2006, in patients who had been treated with infliximab (n=40), etanercept (n=37), and adalimumab (n=15).\textsuperscript{19}

Several mechanisms have been implicated in DILE, including genetics and auto-antibody production. Agents such as procainamide, hydralazine, and isoniazid generally cause DILE in patients with genetic abnormalities. These medications all undergo acetylation as part of their metabolism, so patients who are slow acetylators tend to have more problems with DILE compared with those who have normal or fast acetylation. Another potential cause of DILE involves hapten-like reactions where the drug or its metabolites bind to proteins rendering them foreign to the body. This in turn leads to an autoimmune response by the body. Other drugs, like the anti-TNF agents, are thought to produce auto-antibodies by causing direct damage to the immune system.\textsuperscript{8–10}

**DIAGNOSIS AND CLINICAL PRESENTATION**

Diagnosis is based on classification criteria established by the American College of Rheumatology (ACR). A minimum of 4 of the 11 ACR criteria should be met in order to qualify as SLE for clinical trials. The 11 ACR criteria are broken into systems: cutaneous, musculoskeletal, nonerosive arthritis, cardiopulmonary pleuritis or pericarditis, renal, neurological disorder with seizures or psychosis due to unknown causes, and laboratory.\textsuperscript{20} A rheumatologist or nephrologist may diagnose a patient if the patient meets only 3 of the criteria (1 must be clinical and 1 must be serologic) and has other clinical manifestations such as alopecia, skin vasculitis, Raynaud’s phenomenon, or lung fibrosis.\textsuperscript{3} Some patients may have only 1 organ system involved or only have some of the manifestations of SLE and will, therefore, not be diagnosed with SLE under the ACR criteria. These patients are classified as having “incomplete” or “latent” lupus.\textsuperscript{16} Furthermore, patients might have SLE for years before enough criteria are met to classify them as having SLE, with a mean of 2 years between first manifestations and final diagnosis.\textsuperscript{2}

The antinuclear antibodies (ANA) test is highly specific with a positive result in >95% of SLE patients. The anti-dsDNA antibody test is positive in 60% of SLE patients and is considered the best marker for disease activity, with a specificity of almost 100%, except in elderly patients who have a lower prevalence of anti-dsDNA.\textsuperscript{14} Anti-Ro (SSA) antibodies with anti-La (SSB) occur in 20% to 30% of patients. SSA are associated with subacute cutaneous lesions and sicca syndrome, and SSB with malar rash, subacute cutaneous lesions, photosensitivity, arthritis, serositis, and thrombosis. Anti-U1-snRNP occurs in 13% of patients, and anti-Sm antibodies occur in 10% of patients, especially those with oral ulcers and myositis.\textsuperscript{2} Up to 95% of patients with DILE have positive anti-histone antibodies. Therefore, these patients generally have positive ANA with a homogenous anti-histone staining pattern.\textsuperscript{10} In addition to blood work, renal biopsy is needed for those patients who develop renal complications in order to classify severity (see Table 2, page 181, for the World Health Organization [WHO] classification) and to determine if treatment is warranted.\textsuperscript{21}

Clinical presentation can include nonspecific symptoms (eg, severe fatigue, fever, weight loss, and lymphadenopathy). Common skin manifestations include a malar or butterfly rash, with sun-induced macules or papules occurring on the face, or a generalized rash occurring on the body, which may or may not be sun induced. Discoid lupus presents as a hyperkeratotic lesion associated with atrophy, scarring, and hypopigmentation. Ninety percent of patients have joint inflammation such as arthralgia, arthritis, tendinitis, or early morning stiffness generally in the knees, wrists, and hands. Joint inflammation tends not to cause permanent damage. Men with SLE tend to have less arthritis, but serositis can be more predominant than in women.\textsuperscript{5}

Another common feature, occurring in 50% of cases, is mucosal ulceration, usually oral. Since methotrexate can also cause these ulcerations, it can be difficult to determine if the ulceration is induced by SLE or the drugs used to treat it. Diffuse alopecia can generally occur when the disease is active and is usually reversible during
Table 1

Some medications associated with DILE

<table>
<thead>
<tr>
<th>Drugs with a definitive high risk</th>
<th>Drugs with a definitive low-moderate risk</th>
<th>Drugs with a possible low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide b</td>
<td>Quinidine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Hydralazine c</td>
<td>Methyl dopa</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Penicillamine</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Propythiouracil</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>Acebutolol</td>
<td></td>
</tr>
</tbody>
</table>

*a Several other medications have either a very low risk or have only been suggested to be associated with DILE

*b Up to 20% of patients with DILE with this medication

*c Up to 8% of patients with DILE with this medication

remission. Patchy alopecia, on the other hand, may lead to scarring and can become permanent.5 Cardiovascular and respiratory symptoms are also common and include chest pain on inspiration due to pleurisy or pericarditis. Cardiovascular disease (eg, myocardial infarction) is secondary to accelerated atherosclerosis and other risks (hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes, and heart failure), which can also exacerbate cardiovascular disease in SLE. The risk of hospitalization for an acute myocardial infarction was 2.27 times greater for lupus patients aged 18 to 44 years than for non-lupus patients.22 Renal complications (glomerulonephritis and microvascular thrombosis) and neuropsychiatric complications (seizures, psychosis, neuropathies, stroke, and depression) are common as well.23 Ophthalmic and gastrointestinal manifestations are usually uncommon but can be serious, including keratoconjunctivitis sicca, pancreatitis, hepatitis, and subacute bowel obstruction.

Age at onset affects clinical presentation. Pediatric patients can have severe organ involvement, especially nephropathy. Neurologic and hematologic manifestations such as thrombocytopenia and hemolytic anemia are common early features in pediatric SLE, whereas skin and joint manifestations are less common.2 Arthritis, fever, serositis, sicca symptoms, Raynaud’s syndrome, lung disease, and neuropsychiatric symptoms are more common in the elderly population with SLE, while malar rash, discoid lupus, and glomerulonephritis are less common.4

DILE can present with different clinical features. Symptoms in DILE are generally milder, with arthralgia often being the only symptom that these patients have. Arthralgia and myalgia are both common, occurring in 90% and 50% of patients, respectively. Other common symptoms include fever, pleurisy, and pericarditis. Skin manifestations are relatively uncommon; however, purpura, erythema nodosum, and erythematous papules can be seen. Additionally, renal and central nervous system (CNS) damage do not occur in the vast majority of cases. Onset of most symptoms generally occurs 4 to 20 weeks after initiation of therapy, but some cases of DILE have occurred after years of therapy.8-10

MEASURING TREATMENT OUTCOMES

Disease activity. SLE activity has 3 patterns: flare, chronic, and long quiescence. A flare or relapsing remission is an exacerbation that occurs suddenly and unpredictably; patients are usually in good health between flares. Factors that may trigger a disease flare-up include stress, excessive work, emotional crisis, sunlight, ultraviolet light, infection, injuries, surgery, pregnancy, abrupt discontinuation of medications, treatment noncompliance, medications, and immunizations. Serologic tests are not helpful in predicting flares because serologic activity of SLE may occur without clinical manifestations. Chronic SLE has persistent activity of some type such as chronic synovitis, chronic cytopenias, or active discoid lupus. This chronic activity may or may not require treatment. Patients with long quiescence have a long remission period before having additional flare-up.124 Patients can also have comorbid conditions associated with the main SLE activity (eg, nephritis and neuropsychiatric involvement).

Outcome measures. Disease activity may be measured with validated instruments such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI, the British Isles Lupus Assessment Group scale (BILAG), the European Consensus Lupus Activity Measure (ECLAM), or the Systemic Lupus Activity Measure (SLAM), which are good predictors of damage, reversible inflammation, and mortality. The European League Against Rheumatism (EULAR) Task Force on SLE recommends that at least 1 of these indices be used to monitor disease activity.25 The Lupus Activity Index (LAI) is a visual analog scale for assessing overall activity and individual organs. The Systemic Lupus International Cooperating Clinics/ACR (SLICC/ACR) Damage Index documents the number of items of irreversible organ damage that have occurred.26 To measure health status, the health-related quality of life (HRQOL) or 36-
Ultraviolet A (UVA) and UVB rays. Protecting skin and sunscreens that block both ultraviolet A (UVA) and UVB rays is important. Patients should be instructed to avoid direct exposure to sunlight and use protective clothing and sunscreens that block both ultraviolet A (UVA) and UVB rays. All patients with SLE should practice proper sun protection as appropriate.

Follow-up. Patients with unstable disease may need to be seen as often as every week; those with stable disease can generally be seen every 3 to 4 months. Physical examination includes skin, mucous membranes, lymph nodes, chest, heart, abdomen, extremities, and the musculoskeletal and neurologic systems. Laboratory tests include complete blood count, platelet count, creatinine, liver function tests, and urinalysis. Other monitoring may be required based on the patient’s treatment regimen and specific organ system involvement. Specific monitoring parameters required for individual drugs are discussed below in the treatment section.

Nonpharmacologic Management
There is little, if any, literature on nonpharmacologic management of SLE. Despite the lack of evidence, EULAR and ACR guidelines do make some recommendations. All patients with SLE should practice proper sun protection as approximately one-third of patients are photosensitive. Patients should be instructed to avoid direct exposure to sunlight and use protective clothing and sunscreens that block both ultraviolet A (UVA) and UVB rays. Patients should also be counseled to avoid tanning beds. This is especially important for patients with cutaneous involvement. Smoking cessation is also recommended for all patients with SLE because current smokers have been shown to have significantly higher SLEDAI scores than previous smokers or never smokers. It is also important that patients maintain proper nutrition, including adequate intake of calcium and vitamin D. These are especially important in patients receiving long-term glucocorticoid therapy. Vitamin D levels should be monitored periodically as well, since patients are encouraged to avoid sun exposure, which could cause problems with inadequate conversion of vitamin D in the skin. In addition, it is recommended that patients exercise routinely. Patients may also need other individualized nonpharmacologic therapy based on the different comorbid conditions that may be present (such as diet and exercise recommendations for patients with cardiovascular disease).

Pharmacologic Treatments
Guidelines were developed by the ACR in 1999 and the EULAR taskforce in 2008. These are the most commonly used guidelines but do have some limitations, particularly the ACR guidelines, because of the outdated nature of the material. Newer medications are not included in the guidelines because they were not available.

SLE treatment is highly individualized and depends on symptom manifestations, organ involvement, and disease severity. Duration of therapy is also highly individualized and is based on the patient’s response. Antimalarials and nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in the treatment of mild symptoms such as arthralgias and cutaneous manifestations. Oral corticosteroids and cytotoxic agents are used in more severe disease. Other medications (cyclophosphamide, immunosuppressive agents, tacrolimus) may be used depending on the severity and various organ systems involved. Belimumab is a newer agent that is approved for patients with mild to moderate disease currently taking standard therapy.

NSAIDs. NSAIDs are commonly prescribed for patients with SLE because greater than 90% will develop arthralgias or polyarthralgia. Because there are limited data to support improved outcomes in SLE, NSAIDs should be used cautiously, and there are significant risks associated with long-term use. NSAIDs work by inhibiting cyclooxygenase-2 (COX-2), which inhibits the production of prostaglandins that mediate inflammation and pain. In addition to COX-2 inhibition, NSAIDs can also inhibit COX-1, which in turn inhibits the production of prostaglandins that protect the lining of the gastrointestinal tract. Therefore, gastrointestinal bleeding is a concern, especially in patients who are taking these medications long term and/or receiving corticosteroids. It is therefore recommended to use an NSAID with higher COX-2 selectivity, such as celecoxib, and to avoid agents with less selectivity such as piroxicam and ketorolac. Additionally, patients on long-term NSAIDs may require a proton-pump inhibitor or histamine-2 receptor blocker to help prevent complications and alleviate side effects.

Patients requiring long-term therapy should have a complete blood count and serum creatinine level measured annually and be instructed on how to monitor for signs/symptoms of bleeding (unusual bleeding, bloody stools, and blood in the urine).

Antimalarials. Antimalarials are used to treat and prevent flares and are particularly useful for arthralgias that are not adequately controlled with NSAIDs. They may also be useful in patients with cutaneous manifestations.

Table 2
Lupus nephritis classification

| II  | Normal glomeruli                      |
| III | Pure mesangial alterations           |
| IV  | Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations) |
| V   | Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation and/or extensive subendothelial deposits) |
| VI  | Diffuse membranous glomerulonephritis |
| VII | Advanced sclerosing glomerulonephritis |

Formulary/Source: Ref 21
Hydroxychloroquine is the most commonly prescribed antimalarial agent, accounting for up to 95% of the prescriptions in the United States. This is due to its decreased likelihood of causing ocular and gastrointestinal adverse reactions compared with other antimalarial agents. Hydroxychloroquine has also been shown to help maintain remission, possibly protect against vascular and thrombotic events, and to improve lipid levels. Chloroquine is another antimalarial agent that can be used.

The mechanism of action of antimalarial agents in the treatment of SLE is not fully understood but is believed to be due to their known immunosuppressive and anti-inflammatory properties. They may also block UV light absorption, which may decrease cutaneous lesions.

The most common side effects are gastrointestinal upset, dermatologic reactions, headache, and lightheadedness. Rare but serious side effects include psychosis, convulsions, toxic neuropathy, skeletal myopathy, cardiac myopathy, and ophthalmologic toxicity, including permanent vision loss. The ACR recommends that all patients undergo a baseline eye examination before beginning treatment with an antimalarial agent, followed by ophthalmologic assessments every 6 to 12 months. The American Academy of Ophthalmology in 2002 published recommendations for retinopathy screening. They base their recommendations on the economical burden of frequent screening, risk level of the patient, and duration of antimalarial treatment. Since there are no standardized screening parameters, they recommend following the recommendations from the American Academy of Ophthalmology Preferred Practice Pattern based on the patient’s age if they do not have risk factors.

**Glucocorticoids.** Systemic glucocorticoids used alone or in combination with other immunosuppressive agents are typically reserved for patients with significant organ involvement, particularly renal or CNS. High doses (40 to 60 mg/d of prednisone or prednisone equivalent) are used in patients with severe SLE, while doses of 10 mg/d or less are used for milder SLE for treatment of cutaneous and musculoskeletal symptoms not responding to other therapies. Doses and dosage forms may vary based on severity and complications but the shortest duration possible should be used to avoid long-term complications with these medications, which may include myopathy, osteoporosis, hypertension, diabetes, atherosclerotic vascular disease, and infections. Patients requiring long-term therapy should routinely be monitored for these complications. Total cholesterol and bone density should be checked annually, and blood glucose levels should be checked every 3 to 6 months.

**Cytotoxic/immunosuppressive agents.** Patients who are not responsive to antimalarials or glucocorticoids should be considered for treatment with immunosuppressive agents for more severe manifestations of the disease. Agents in this category include cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate. The majority of data with these agents are in the area of SLE nephritis. It is important to note that mycophenolate mofetil, cyclophosphamide, azathioprine, and methotrexate must be avoided during pregnancy. Some of these agents have also shown promise in neuropsychiatric symptoms as well as in severe cutaneous manifestations of lupus.

The intravenous route of administration of cyclophosphamide is generally preferred due to fewer side effects compared with oral administration. Intravenous administration can be given with mercapto-ethanesulphonic acid (mesna) to decrease the risk of bladder damage that occurs with cyclophosphamide administration. Mycophenolate has shown promise as compared with cyclophosphamide; however, long-term data are lacking, so cyclophosphamide is preferred in combination with steroids for proliferative nephritis.

Several other agents have been tried for patients with more severe and resistant disease, including fludarabine and cladribine. Much of the evidence for these agents is from anecdotal, uncontrolled trials or very small controlled trials. Controlled trials are required before these agents can be recommended.

**Belimumab.** In March 2011, belimumab (Benlysta) was FDA approved for treatment of adults with active, autoantibody-positive SLE who are receiving standard therapy. Belimumab has a unique mechanism of action targeting B-cell dysfunction by inhibiting B-lymphocyte stimulator (BLyS). It has been shown that decreases in BLyS levels are associated with improvement in SLE activity and increases in BLyS levels are associated with worsening SLE activity and mild/moderate flares.

Belimumab’s safety and efficacy have been evaluated in 3 randomized, double-blind, placebo-controlled studies. In all 3 studies, patients met ACR criteria for SLE and were on standard SLE therapies including corticosteroids, antimalarials, NSAIDs, and immunosuppressants (alone or in combination). Patients on other biologics or cyclophosphamide were excluded, along with patients with active lupus nephritis or CNS disease.

The phase 2 study included patients who had a history of measurable autoantibodies and had coprimary outcomes of percent change in the SELENA-SLEDAI score and time to first mild/moderate or severe flare. In the study population as a whole, belimumab was well tolerated but did not significantly reduce SLE disease activity or flares. When the subgroup of seropositive patients (71.5% of population) was evaluated, they had a significantly improved response. This led to the evaluation and development of a novel composite end point called the SLE Responder Index (SRI) to be used as the primary end point in both phase 3 studies. The SRI uses the SELENA-SLEDAI score to determine global improvement, BILAG scores to assure no worsening...
For the treatment of adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria, as indicated below.

Discover a NEW IV Cephalosporin for

COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

CABP

AND

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

ABSSSI

INDICATIONS

- TEFLARO™ is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Streptococcus pneumoniae (including cases with concurrent bacteremia), Staphylococcus aureus (methicillin-susceptible isolates only), Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca, and Escherichia coli.

- TEFLARO is also indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Staphylococcus aureus (including methicillin-susceptible and -resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.

IMPORTANT SAFETY INFORMATION

Contraindications

- TEFLARO is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement. Please also see full Prescribing Information at www.TEFLARO.com.
Introducing TEFLARO™

BROAD-SPECTRUM cephalosporin coverage

INDICATIONS AND USAGE

- TEFLARO is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Streptococcus pneumoniae (including cases with concurrent bacteremia), Staphylococcus aureus (methicillin-susceptible isolates only), Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca, and Escherichia coli.

- TEFLARO is also indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Staphylococcus aureus (including methicillin-susceptible and -resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.

- If an allergic reaction to TEFLARO occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

Clostridium difficile-associated Diarrhea

- Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against C. difficile should be discontinued, if possible.
Broad-spectrum coverage for treating CABP and ABSSSI

Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including S. pneumoniae in CABP and MRSA in ABSSSI

Proven efficacy in 2 common infections in patients admitted to the hospital

- Convenient q12h dosing in CABP and ABSSSI'
  - 600 mg intravenous over 1 hour
  - Treatment duration
    › 5-7 days for CABP
    › 5-14 days for ABSSSI

IMPORTANT SAFETY INFORMATION
Direct Coombs' Test Seroconversion
- Seroconversion from a negative to a positive direct Coombs’ test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

Development of Drug-Resistant Bacteria
- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.
TEFLARO CABP Study Designs

- **Type of trial:** Two randomized, multicenter, multinational, double-blind, noninferiority trials
- **Study population:** 1231 adults with a diagnosis of CABP
- **Comparative agents:**
  - TEFLARO: 600 mg administered IV over 1 hour every 12 hours for 5-7 days
  - Ceftriaxone: 1 g ceftriaxone administered IV over 30 minutes every 24 hours for 5-7 days
- **Adjunctive therapy:**
  - CABP Trial 1, two doses on Day 1 of oral clarithromycin 500 mg every 12 hours
  - CABP Trial 2, no adjunctive macrolide therapy

### TEFLARO Study Populations

<table>
<thead>
<tr>
<th>Test of Cure (TOC) Populations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT Modified Intent-to-treat</td>
<td>All randomized subjects who received any amount of study drug.</td>
</tr>
<tr>
<td>MITTE Modified Intent-to-treat Efficacy</td>
<td>All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.</td>
</tr>
<tr>
<td>CE Clinically Evaluable</td>
<td>All subjects in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient's outcome.</td>
</tr>
<tr>
<td>ME Microbiologically Evaluable</td>
<td>All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (e.g., blood, sputum, or pleural fluid).</td>
</tr>
</tbody>
</table>

*To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to be both (a) in stable condition according to consensus treatment guidelines, and (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.

The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary MITT and CE populations and clinical cure rates at TOC by pathogen in the ME population.

**INDICATION AND USAGE**

- **TEFLARO** is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria.

**IMPORTANT SAFETY INFORMATION**

**Adverse Reactions**

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.

- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.
**TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia**

<table>
<thead>
<tr>
<th>Treatment Difference 11.2 (95% CI: -4.6, 26.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong> 69.6% (48/69)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> 58.3% (42/72)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Difference 7.6 (95% CI: -6.8, 21.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong> 69.0% (58/84)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> 61.4% (51/83)</td>
</tr>
</tbody>
</table>

Clinical response, % (n/N)

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

**TEFLARO Demonstrated Efficacy at TOC† (CE) in Community-Acquired Bacterial Pneumonia**

<table>
<thead>
<tr>
<th>Treatment Difference 8.4 (95% CI: 1.4, 15.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong> 86.6% (194/224)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> 78.2% (183/234)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Difference 5.2 (95% CI: -2.2, 12.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong> 82.3% (191/232)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> 77.1% (165/214)</td>
</tr>
</tbody>
</table>

Clinical cure rates, % (n/N)

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

Patients with known or suspected MRSA were excluded from both trials.

†FOCUS= Ceftraroline Community-Acquired Pneumonia Trial vs Ceftriaxone in Hospital Patients. FOCUS 1=CABP Trial 1, FOCUS 2=CABP Trial 2.

There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish noninferiority.

**IMPORTANT SAFETY INFORMATION**

**Drug Interactions**

- No clinical drug-drug interaction studies have been conducted with TEFLARO. There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.
Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design1-3

| Type of trial:                  | Two identical, randomized, multicenter, multinational, double-blind, noninferiority trials |
| Study population:              | 1396 adults with clinically documented complicated skin and skin structure infection |
| Comparative agents:            | TEFLARO — 600 mg administered IV over 1 hour every 12 hours for 5-14 days; Vancomycin plus aztreonam — 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 30 minutes for 5-14 days |
| Treatment duration:            | Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed |

### TEFLARO Study Populations

<table>
<thead>
<tr>
<th>Day 3 Population*</th>
<th>The analysis evaluated patients with lesion size ≥75 cm² and having one of the following infection types:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Major abscess with ≥5 cm of surrounding erythema</td>
</tr>
<tr>
<td></td>
<td>- Wound infection</td>
</tr>
<tr>
<td></td>
<td>- Deep/extensive cellulitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test of Cure (TOC) Populations†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT</td>
<td>Modified Intent-to-treat All randomized subjects who received any amount of study drug.</td>
</tr>
<tr>
<td>CE</td>
<td>Clinically Evaluable Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluability criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject's outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.</td>
</tr>
<tr>
<td>ME</td>
<td>Microbiologically Evaluable This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.</td>
</tr>
</tbody>
</table>

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.

† The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary CE and MITT populations and clinical cure rates at TOC by pathogen in the ME population.

### INDICATION AND USAGE

- **TEFLARO** is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI that is proven or strongly suspected to be caused by susceptible bacteria.

### IMPORTANT SAFETY INFORMATION

#### Use in Specific Populations

- TEFLARO has not been studied in pregnant women. Therefore, TEFLARO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEFLARO is administered to a nursing woman.

- Safety and effectiveness in pediatric patients have not been established.

- Because elderly patients, those ≥65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.

- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤50 mL/min) or severe (CrCl ≥15 to ≤30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).

- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.
### TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Responders, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEFLARO monotherapy</td>
<td>74.0% (148/200)</td>
</tr>
<tr>
<td>Vancomycin + aztreonam</td>
<td>64.6% (135/209)</td>
</tr>
</tbody>
</table>

Treatment Difference 9.4 (95% CI: 0.4, 18.2)

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

### TEFLARO Demonstrated Efficacy at TOC (CE) in Acute Bacterial Skin and Skin Structure Infections

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Cure Rates, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEFLARO monotherapy</td>
<td>91.1% (288/316)</td>
</tr>
<tr>
<td>Vancomycin + aztreonam</td>
<td>93.3% (280/300)</td>
</tr>
</tbody>
</table>

Treatment Difference 2.2 (95% CI: -6.6, 2.1)

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

---

*CANVAS = Ceftaroline vs Vancomycin in Skin and Skin Structure Infection. CANVAS 1 = ABSSSI Trial 1, CANVAS 2 = ABSSSI Trial 2.

1There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.


Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.
Table 3
Summary of cytotoxic/immunosuppressive medications used in the treatment of lupus nephritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Immunosuppressive prodrug—prevents cell division</td>
<td>• 500–1,000 mg/m² IV infusion once per mo</td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nephritis: 500–1,000 mg/m² IV infusion for 6 mo, then quarterly for 18 mo</td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral: max 2 mg/kg/d for max of 6 mo</td>
<td>• Bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bladder carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lymphoma, leukemia, skin malignancies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bladder cancer (more with oral than IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pregnancy category D</td>
</tr>
<tr>
<td>Methotrexate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Immunosuppressive—dihydrofolic acid reductase inhibitor</td>
<td>• 7.5–15 mg once a wk</td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Abdominal distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ulcerative stomatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Leukopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fatigue/malaise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Dehydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Acute and chronic hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lung disease</td>
</tr>
<tr>
<td></td>
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<td>• Lymphoma</td>
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<td>• Severe skin reactions</td>
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<td>• Opportunistic infections</td>
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<td>• Pregnancy category X</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>Immunosuppressive prodrug—inosine monophosphate dehydrogenase inhibitor</td>
<td>• 1 g twice a day for 6 mo, then 0.5 g twice a day for 6 mo, has been used&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Diarrhea</td>
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<td>• Anemia</td>
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<td>• Leukopenia</td>
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<td>• Thrombocytopenia</td>
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<td></td>
<td>• Infections (cytomegalovirus and herpes)</td>
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<td>• Pregnancy category D</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Immunosuppressive—mercaptopurine derivative</td>
<td>• 1–2 mg/kg/m² are typically used in studies up to 4 mg/kg/m²&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Leukopenia</td>
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<td>• Fever/malaise</td>
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<td>• Myalgias</td>
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<td>• Pregnancy category D</td>
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Abbreviation: IV, intravenous; mo, month; d, day; wk, week

<sup>a</sup> When used in combination with NSAIDs may cause severe bone marrow suppression, aplastic anemia, and gastrotoxicity

<sup>b</sup> Most common regimen used for lupus nephritis. The dose has not been clearly defined.

Formulary/Source: Refs 36,38,39,47–50
in a particular organ system, and physician's global assessment scores.44 The phase 3 trials (BLISS-5245 and BLISS-7646) included only patients who were seropositive at screening, and both trials used SRI response rate at week 52 as their primary end point. BLISS-52 (n=865) and BLISS-76 (n=819) randomized patients to standard of care plus placebo, belimumab 1 mg/kg, or belimumab 10 mg/kg for 52 weeks or 76 weeks, respectively. Both studies showed significant improvement in patient response according to the SRI using the belimumab 10 mg/kg dose compared with placebo at week 52; there was a 57.6% versus 43.6% response rate, respectively (P=0.0006), in BLISS-52 and 43.2% versus 33.5% response rate, respectively (P=0.017), in BLISS-76. The numbers needed to treat for the BLISS-52 and BLISS-76 were 8 and 11, respectively. The 76-week results from BLISS-76 failed to show a statistically significant difference between belimumab 10 mg/kg compared with placebo in the percentage of patients responding according to the SRI (38.5% vs 32.4%, respectively; P=0.13). Safety data through week 76 showed that belimumab was generally well tolerated, with rates of adverse events, infections, and discontinuation that were similar to placebo.46

TREATMENTS FOR SPECIFIC DISEASE MANIFESTATIONS OR PRESENTATIONS

Lupus nephritis. Patients with a WHO Class I/II nephritis generally have a good prognosis and simply require monitoring for worsening of symptoms. Those with WHO Class III/IV generally have a very poor prognosis and require aggressive treatment. With appropriate treatment, the 5-year survival rate for these patients can be over 90%. Detailed information on common medications used in SLE nephritis is shown in Table 3 (page 191). Treatment of lupus nephritis consists of 2 phases: induction and maintenance. There is some controversy as to what agent should be used due to issues with the individual agents and limited data, particularly with maintenance therapy. Selection of the appropriate agent depends on the severity of disease, risk of adverse reactions with the different medications, desire to preserve fertility, and cost. Typically, patients will be started on a regimen of IV cyclophosphamide plus corticosteroids or mycophenolate mofetil. Meta-analyses of lupus nephritis therapies have generally shown that there is similar efficacy between mycophenolate mofetil and cyclophosphamide for induction therapy. Studies included in these analyses generally lasted between 6 and 12 months.

Cyclophosphamide in addition to corticosteroids has been shown to improve renal function by decreasing the risk of doubling serum creatinine levels (RR, 0.59; 95% CI, 0.4–0.88) and of relapsing (RR, 0.3; 95% CI, 0.1–0.94) when compared to steroids alone. They have, however, failed to show an improvement in mortality. Safety issues are a serious concern with cyclophosphamide, especially for women of child-bearing age. The risk of ovarian failure was significantly increased when cyclophosphamide was added to steroids compared with steroids alone (RR, 2.18; 95% CI, 1.1–4.34). Patients with proliferative renal disease should also receive standard therapy for chronic kidney disease including angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists and lipid-lowering therapies. Patients with more mild disease, however, was increased with mycophenolate mofetil plus steroids compared to cyclophosphamide plus steroids (RR, 2.98; 95% CI, 1.1–8.11). According to the EULAR guidelines, more intensive therapy may be needed if patients do not have significant improvement (improvement in serum creatinine and reduction of proteinuria to <1 g/d) after 6 months of treatment. Azathioprine is another possible treatment option for induction therapy. When added to steroids, it decreased all-cause mortality (RR, 0.6; 95% CI, 0.36–0.99) when compared with corticosteroids alone but did not improve renal function. Azathioprine did not increase the risk of ovarian failure. Triple combination therapy with cyclophosphamide, azathioprine, and steroids is not recommended since the only benefit seen was an improvement in the risk of having the serum creatinine double.

Studies examining long-term maintenance therapy are limited. The MAINTAIN trial was designed to compare the long-term effects of mycophenolate mofetil and azathioprine. Patients had WHO class III–V renal disease and met ACR criteria for SLE. Patients were randomized to the azathioprine (azathioprine + glucocorticoids + cyclophosphamide) or mycophenolate mofetil groups (mycophenolate mofetil + glucocorticoids + cyclophosphamide) and were followed for an average of 48 months. There was no difference in the time to renal flare (HR, 0.75; 95% CI, 0.33–1.71 for mycophenolate compared with azathioprine). Adverse reactions were similar among the groups.

Cutaneous lupus erythematosus. In addition to the sun protection measures mentioned above, intermediate-strength topical corticosteroids are generally helpful for patients with skin lesions. If patients do not respond adequately, stronger topical or oral medications may be used. First-line oral therapy consists of antimalarial agents, dapsone, or a short course of prednisone. If these treatments fail, then treatment can move on to isotretinoin or gold compounds. For more severe, resistant cases, methotrexate, cyclophosphamide, cyclosporine, or long-term corticosteroids can be tried. Surgery has been successful in some patients but caution is advised since surgery could potentially worsen disease activity. Agents that have recently been tried include thalidomide, mycophenolate mofetil, and intravenous immune globulin. Controlled trials are needed to determine
the place of these agents in therapy. Tacrolimus and pimecrolimus have also shown promise in treating skin lesions. Tacrolimus when compared to clobetasol showed a decrease in side effects with a similar efficacy profile. Both tacrolimus and pimecrolimus have shown improvement within a few weeks after initiation of therapy. Tacrolimus showed improvement in photosensitive rash, and pimecrolimus showed improvement in cutaneous lesions. Both medications also appear efficacious in subacute cutaneous lupus erythematosus. For discoid lupus, pimecrolimus appears to be more effective than tacrolimus. The main issue regarding these medications is that they have not been compared to other agents in a controlled manner. Controlled studies are needed to determine what role these agents may play in treating cutaneous symptoms.

Neuropsychiatric lupus. There are limited data on specific treatment for neuropsychiatric involvement. Treatment usually focuses on the psychiatric symptoms rather than on treating the lupus (eg, anticonvulsants to treat seizures or antidepressants for patients with depressive symptoms). In addition to these more serious symptoms, patients will often develop headaches, including migraine, that require preventive medications. There is some evidence to suggest that rituximab may be useful in these patients as well, but controlled trials are needed to confirm this.

One randomized controlled trial has been conducted comparing cyclophosphamide and methylprednisolone for the treatment of neuropsychiatric symptoms in patients with lupus. A statistically significant difference was seen between the groups with 18 of 19 patients in the cyclophosphamide group compared with 6 of 13 patients in the methylprednisolone group responding at 24 months (RR, 2.05; 95% CI, 1.13–3.73). Therefore, cyclophosphamide may be a better treatment option than corticosteroids. A risk/benefit analysis is needed before recommending cyclophosphamide in individual patients, due to the significant risk of adverse reactions.

Drug-induced lupus. Treatment of DILE is primarily withdrawal of the offending agent. Symptoms will generally start to resolve within a few days to weeks after discontinuation. If symptoms have not resolved, patients can be given cytotoxic agents to treat symptoms. Corticosteroids should be reserved for patients with organ damage. Patients who do not have complete resolution of symptoms should be worked up for development of idiopathic SLE, since some medications may just expose an underlying case rather than causing DILE.

Pipeline
Several agents have recently been or are currently being evaluated for safety and efficacy in lupus. Many of these medications have failed to show a difference when compared to placebo or standard therapy, while others are still in the early stages of clinical trial testing. Leftunomide has shown some promising results in clinical trials. Rituximab is another agent that has some limited data to suggest that it may be beneficial in patients with SLE nephritis. Clinical trials with rituximab are currently underway or have reached completion, and will help to define its role in therapy.

Conclusion
Systemic lupus erythematosus is an autoimmune disorder that can affect several organ systems, including the skin, kidneys, and CNS. Better and earlier recognition of SLE and more effective treatments have significantly improved survival rates. Treatment is generally individualized, based on clinical presentation of the patient. The main nonpharmacologic management strategies are proper sun protection (eg, avoidance, protective clothing, and sunscreen with both UVA and UVB protection) and proper nutrition. Glucocorticoids, NSAIDs, cytotoxic/immunosuppressive agents, and antimarial agents are used for generalized symptoms and patients with more chronic or severe symptoms. Lupus nephritis is one of the most common manifestations and is generally treated with a combination of cyclophosphamide and corticosteroids. Other disease manifestations may be treated with therapy targeting the specific condition, such as antipsychotic medications for psychiatric symptoms.

REFERENCES
FDA cautions prescribers of risk for severe immune-mediated adverse reactions with ipilimumab use

On April 6, 2011, FDA released a safety communication alerting healthcare providers to a new risk evaluation and mitigation strategy (REMS) for ipilimumab (Yervoy, Bristol-Myers Squibb).

The currently available prescribing information for ipilimumab contains a black-boxed warning stating that use of the product can result in severe and fatal immune-mediated adverse reactions.

According to FDA, the ipilimumab REMS will consist of a communication plan to inform healthcare professionals of the serious risks of ipilimumab in order to facilitate early identification of these risks, and recommendations for management of patients with moderate or severe immune-mediated adverse reactions including enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.

During the randomized, double-blind clinical study supporting ipilimumab’s marketing approval, a severe to fatal immune-mediated adverse reaction occurred in approximately 11% of the 511 patients studied. These events were most commonly enterocolitis (~7%), followed by dermatitis (~3%), endocrinopathy (~2%), hepatotoxicity (<2%), and neuropathy (<1%). Most immune-mediated reactions initially occurred during ipilimumab treatment (typically at a dose of 3 mg/kg every 3 weeks for a total of 4 doses); however, a minority occurred anywhere from weeks to months after treatment discontinuation.

According to the drug’s prescribing information and FDA release, immune-mediated hepatitis and endocrinopathies should be monitored prior to each dose of ipilimumab. If a severe case of immune-mediated reaction occurs, ipilimumab should be permanently discontinued. For moderate immune-mediated adverse reactions, it is recommended that ipilimumab be withheld until the patient returns to baseline, the reaction improves to a mild severity or complete resolution is achieved, and patient is receiving <7.5 mg prednisone or equivalent per day. High-dose systemic corticosteroids are recommended for patients experiencing a severe, persistent, or recurring immune-mediated reaction.

PPIs’ efficacy and safety questioned for pediatric GERD

The effectiveness and safety of proton pump inhibitors (PPIs) for pediatric gastroesophageal reflux disease (GERD) are far from proven, according to a new systematic review published on-line, ahead-of-print in *Pediatrics*.

Despite this, lead author Rachel van der Pol, MD, from the department of pediatric gastroenterology and nutrition, Emma Children’s Hospital AMC, Amsterdam, Netherlands, said, “Use of PPIs for the treatment of GERD in children has increased enormously.”

Six-month costs of pediatric GERD are estimated to exceed $2,300 per patient. Dr van der Pol and co-investigators conducted a systematic literature review of the PubMed, Embase, and Cochrane databases in an attempt to unearth all available randomized controlled trials investigating the efficacy and safety of PPIs in children (aged 0 to 18 years) with GERD. Ultimately, the investigators identified 12 eligible trials enrolling a total of 895 patients. PPIs evaluated in eligible studies included omeprazole, esomeprazole, pantoprazole, and lansoprazole.

Based upon results of 5 randomized trials, 4 of which on their own did not support the efficacy of PPIs, the investigators concluded that these drugs are not effective in reducing GERD symptoms in infants. The authors stressed, “If the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed.”

Furthermore, the researchers noted that while there is a lack of placebo-controlled trials in children and adolescents, available data comparing PPIs to active controls such as alginate and histamine-2 receptor blockers suggests these anti-secretory agents are no more efficacious than comparators.

PPI safety in the pediatric population was also evaluated in this literature review. Authors commented that short-term PPI use appeared well tolerated, “but evidence to ensure safety is still lacking.”

Taken together the findings prompted investigators to recommend, “…physicians should be careful when prescribing PPIs, medications that are not approved for infants and have potential adverse effects, unless there is documented disease or with careful monitoring.”

The investigators highlighted that there was a paucity of methodologically rigorous, well-designed randomized controlled trials addressing this topic published in the medical literature, and that such trials had only meager sample sizes. The authors concluded by calling for larger randomized controlled trials to be conducted in pediatric patients of every age in order to address what they referred to as “a growing healthcare problem.”
FDA, NIH, pharma companies seek new strategies to spur drug development

Drug development pipelines have shrunk; fewer new products are being approved for market; and pharma companies are scaling back R&D as patent expirations on blockbuster drugs reduce industry revenues.

The situation is prompting a serious search for new business models for new drug development. Manufacturers are looking to partner more with small biotech firms and academic research institutes, to shift research and production operations overseas, and to streamline operations and reduce waste wherever possible. The National Institutes of Health (NIH) proposes to ramp up support for translational medicine that will shepherd basic research through the R&D “valley of death” to yield new therapies. Patient advocacy groups are consulting with and providing funding for public and private therapy development programs. And FDA is eyeing new strategies to improve its application review process.

America’s position as the world leader in biomedical R&D is “under siege today,” facing its biggest threat in 65 years, commented former Congressman John Porter, at a forum in March sponsored by ResearchAmerica. “Is America going to put progress on hold?” he asked in calling for government decision-makers to consider the importance of science and innovation in making federal spending decisions.

SLOWDOWN AT FDA
Some of the blame for longer, more costly drug development falls on the shoulders of FDA. Stepped-up demand for more safety and efficacy data appears to add to development costs, and ultimately to less robust pharmaceutical R&D programs. Moreover, success rates remain notably low for new drugs in clinical development, despite years of efforts to better inform the clinical research process in order to avoid wasting millions of dollars on unsuccessful studies.

Most disappointing is the decline in new drug approvals by FDA last year, a troubling shift after 2 years of slight increases in new drugs moving through the agency.

FDA cleared only 21 new molecular entities (NMEs) in 2010, down from 25 in 2009. The rejections hit several promising experimental products, including new diabetes therapies and weight-loss drugs. Even more discouraging are reports that fewer applications for innovative new therapies were filed with FDA last year, squelching optimism about any upturn in product approvals in the near future.

Yet, several important new therapies made it to market. Amgen won approval for osteoporosis treatment Prolia (denosumab), and Roche’s Genentech brought out Actemra (tocilizumab), an intravenous drug for rheumatoid arthritis. Boehringer Ingelheim won the race to bring to market a new blood-thinner Pradaxa (dabigatran etexilate). Probably the most exciting new product was Dendreon’s therapeutic prostate cancer vaccine Provenge (sipuleucel-T). And new vaccines for meningococcal disease and pneumococcal disease also were approved by the Center for Biologics Evaluation and Research (CBER).

Some more good news has emerged this year. Last month, FDA approved a new treatment for melanoma, Bristol-Myers Squibb’s Yervoy (ipilimumab), touted as the first drug to prolong lives of patients with this deadly skin cancer and a vast improvement over existing therapies. Another high-profile recent approval is the first new treatment for lupus in more than 50 years—Human Genome Sciences’ Benlysta (belimumab).

SEEKING IMPROVEMENT
FDA admittedly is caught in a hard place. Patient advocates demand earlier access to promising therapies, yet policy makers and consumer groups insist on more scrutiny of test products to better detect potential safety problems. Moreover, the agency has struggled in the last few years to implement a host of new requirements established by the FDA Amendments Act (FDAAA) of 2007, which resulted in a slow-down in processing new drug applications.

Now staffers are meeting user fee review goals more steadily as the agency moves into a “period of consolidation,” says Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER). The Center has implemented many FDAAA initiatives, is negotiating a new Prescription Drug User Fee (PDUFA) program, and is establishing a Quality Management System for more efficient 21st-century review process. There also are more first-cycle approvals, a key benchmark for both sponsors and regulators, and the rate of first launches in the United States is holding steady.

The looming reauthorization of PDUFA in 2012 is prompting a re-evaluation of many regulatory and review processes. One area of focus is the Risk Evaluation and Mitigation Strategies (REMS) program, which

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has been criticized by manufacturers and pharmacists for spawning too many diverse REMS formats. Proposals are on the table to reduce REMS controls for only those products that require distribution of medication guides, and to devise common formats for such documents. FDA recognizes, said Woodcock, that REMS requirements should not delay product approvals.

Discussions regarding generic drug user fees, moreover, are moving forward. A main objective for FDA is to gain additional support for more timely plant inspections in face of a notable rise in foreign sourcing of active ingredients as well as generic drug productions.

Another area of focus is FDA’s accelerated approval process, which is designed to avoid delays in moving important new therapies to market. The system has been criticized because manufacturers often fail to complete agreed-on confirmatory trials in a timely manner, and some follow-up studies have shown limited efficacy and serious side effects, as with Roche’s Avastin (bevacizumab). FDA officials have proposed that sponsors launch confirmatory trials before the agency grants fast-track approval to ensure that additional studies are done according to plan.

Greater difficulties in developing new drugs for broad patient populations, such as diabetic and obese patients, are prompting collaborative efforts to better understand approval requirements. Woodcock and her staff recently met with a group of obesity experts to discuss standards for bringing weight-loss drugs to market. Medical experts in the field proposed that regulators consider the broader health benefits of weight-loss, such as reduction in sleep apnea, when assessing potential side effects from drug therapy.

FDA Commissioner Margaret Hamburg continues to stress the importance of advancing regulatory science in order for FDA to be able to support the translation of science into real-world therapies. New biomarkers for toxicology can identify much earlier those drugs likely to fail and also better target therapies to individuals most likely to respond, Hamburg noted. And innovative clinical trial designs can yield answers using fewer patients and less money. The conventional thinking is that new discoveries from biomedical research will lead to new products. But, she explained at the ResearchAmerica forum, there is a regulatory science gap that can prevent new opportunities from coming to fruition.

**PROMOTING TRANSLATION**

The changing biomedical research landscape and cutbacks in industry R&D programs have prompted NIH Director Francis Collins to promote translational medicine as a way to spur development of new biomedical treatments that can benefit patients. In December, an NIH advisory committee recommended establishing a new NIH National Center for Advancing Translational Sciences (NCATS), which aims to bring together a number of NIH programs that provide resources for translating basic discoveries into new medicines and diagnostics, including therapies for rare and neglected diseases.

Collins believes that today there is greater private sector interest in NIH-funded preclinical and clinical testing, as well as in compound rescuing or “repurposing.”

He sees such initiatives as a win-win for pharma companies and for medical research if such a compound was found to be active for a different application than originally considered. NIH will not move into drug development per se, Collins emphasized, but will hand promising compounds off to private sector sponsors.

Collins also hoped that this emphasis on translational science will convince Congress and the American public that the federal investment in biomedical research can pay off in terms of new, life-saving therapies. The Obama administration has proposed a very slight increase in the NIH budget for fiscal 2012, which would just barely maintain current funding levels.

Even during the Republican budget-cutting campaign of the mid-1990s, NIH benefitted from strong GOP advocates on Capitol Hill and largely escaped the chopping block; that kind of support seems to be lacking among current Republican leaders.

As the former director of NIH’s Human Genome Project, Collins is optimistic that new genetic discoveries can chart pathways for discovering new medical treatments, and that the emergence of more well-validated genes will be useful in “identifying drug targets in unprecedented numbers,” he said in an interview.

The scientific enterprise is yielding a lot of new ideas about therapeutics, he observed, yet “traditional private sector efforts to capitalize on that are taking a hammering.” NCATS aims to bolster the funding of research projects at a time when biotech and pharma companies face serious financial challenges. Along these lines, the initiative also will encourage more collaboration between academic researchers and biopharmaceutical companies and to strengthen ties with FDA to ensure that NIH-sponsored studies provide the data needed to support registration of new products.
### New drugs

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<tr>
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<td>Novartis, a melatonin (MT1 and MT2) receptor agonist with 5-HT&lt;sub&gt;2C&lt;/sub&gt; antagonist properties/for the treatment of major depressive disorder (MDD)</td>
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<td>EB-1010</td>
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<td>Euthymics Bioscience, an oral triple reuptake inhibitor with effects on three neurotransmitters—serotonin, norepinephrine, and dopamine/for the treatment of MDD</td>
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<td>F2695/levomilnacipran</td>
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<td>Forest, an oral norepinephrine and serotonin reuptake inhibitor/for the treatment of MDD</td>
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<td>Lu AA21004</td>
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<td>Lundbeck, a 5-HT&lt;sub&gt;1A&lt;/sub&gt; receptor antagonist and 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor agonist and 5-HT enhancer/for the treatment of MDD and generalized anxiety disorder (GAD)</td>
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<td>TC-5214</td>
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<td>Astra Zeneca, a neuronal nicotinic receptor modulator/for the treatment of MDD</td>
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<td>Armodafinil</td>
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### New indications/formulations

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The purpose of Drug Watch is to keep drug decision-makers informed about pharmaceuticals in late-stage development. In each column, 1 or more disease areas or drug classes are presented. The column is researched and compiled by editorial advisory board member Michele B. Kaufman, PharmD, president, PRN Communications, Inc, a consulting/medical writing and editing firm.
The population had a median age of 64 years (range 40-91), 73% were male. 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV1) of 8.9% to 89.1%. In these trials, 66.8% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo. The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%). Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diar rhrea, atrial fibrillation, lung cancer, prostatic cancer, acute pancreatitis, and acute renal failure. Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [see Adverse Reactions (6.1)]. Incidences of suicidal ideation and behavior including completed suicide, the most severe psychiatric reactions, were observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) reported in placebo trials. Before using DALIRESP in patients with a history of depression or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of con tinuing treatment with DALIRESP if such events occur.

Weight Decrease
Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see Adverse Reactions (6.1)]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients receiving placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During long-term discontinuation, the majority of patients who discontinued treatment with DALIRESP had weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [see Clinical Pharmacology (12.3)]. Drugs That Induce Cytochrome P450 (CYP) Enzymes
Strong cytochrome P450 4A5 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effective ness of DALIRESP. Therefore the use of strong cytochrome P450 4A5 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended [see Drug Interactions (5.4) and Clinical Pharmacology (12.3)].

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol
The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enzootic, cotrimoxazole) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. [see Clinical Pharmacology (12.3)].

Drug Interactions
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 4E2 enzyme inducer rifampicin resulted in a reduction of exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong CYP3A4 enzyme inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended. [see Drugs That Induce Cytochrome P450 (CYP) Enzymes]

Liver and Deliver
DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. Therefore, IV drug delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the HRMD (on a mg/m2 basis at a maternal dose of > 2 mg/kg/day) during pregnancy and lactation.

Labor and Delivery
DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. Therefore, IV drug delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the HRMD (on a mg/m2 basis at a maternal dose of > 2 mg/kg/day) during pregnancy and lactation.

Nursing Mothers
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use
DALIRESP does not normally occur in children. The safety and effective ness of DALIRESP in pediatric patients have not been established.

Geriatric Use
The use of DALIRESP in COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 47% were > 75 years of age. No overall differences in safety or efficacy were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses in the elderly and younger patients. Sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted [see Clinical Pharmacology (12.3)].

Hepatic Impairment
Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh B subjects compared to Child-Pugh A subjects, and as compared to age-, weight- and gender-matched healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in heptatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3)].

Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were essentially unchanged. The Cmax was reduced by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in heptatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3)].

OVERDOSAGE
In overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is excreted by human dialysis.

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Indications and Usage
DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION
Contraindications
DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions
- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended.

Adverse Reactions
In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

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