Personalizing Medicine to Transition Oncology Care:
Non-Small Cell Lung Cancer
WHEN PATIENTS PROGRESS, IT’S TIME TO TEST

IN PATIENTS WITH METASTATIC EGFR NON-SMALL CELL LUNG CANCER (NSCLC) WHO HAVE PROGRESSED ON OR AFTER EGFR TKI THERAPY

TAGRISSO HAS THE ONLY FDA-APPROVED, CLINICALLY VALIDATED COMPANION DIAGNOSTIC TEST FOR THE EGFR T790M MUTATION THAT USES EITHER TISSUE OR PLASMA1

Incorporating both tissue and plasma testing into your practice may identify more patients with the EGFR T790M mutation2

• Testing for the presence of the EGFR T790M mutation in plasma specimens is recommended only in patients where tumor tissue is not available3
• If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing3
• The cobas® EGFR Mutation Test v2 was clinically validated based on its results in the TAGRISSO clinical trials1
• Confirm the presence of the EGFR T790M mutation prior to prescribing TAGRISSO3

TAGRISSO DEMONSTRATED EFFICACY IN TWO CLINICAL TRIALS

• Effective in two separate global, Phase II, single-arm, open-label clinical trials in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy3
• A 59% objective response rate (95% CI: 54–64) observed in patients who progressed with previous EGFR TKI therapy3
• Interstitial Lung Disease (ILD) occurred in 3.3% and was fatal in 0.5% of TAGRISSO patients3

TAGRISSO® (osimertinib)

WHEN PATIENTS PROGRESS, 
IT’S TIME TO TEST

IMPORTANT SAFETY INFORMATION

• There are no contraindications for TAGRISSO

• Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

• QTc interval prolongation occurred in TAGRISSO patients. Of the 411 patients in two Phase II studies, 0.2% were found to have a QTc greater than 500 msec, and 2.7% had an increase from baseline QTc greater than 60 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia

• Cardiomyopathy occurred in 1.4% and was fatal in 0.2% of 813 TAGRISSO patients. Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% of (9/375) TAGRISSO patients. Assess LVEF before initiation and then at 3 month intervals of TAGRISSO treatment. Withhold TAGRISSO if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose

• The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please see Brief Summary of complete Prescribing Information on adjacent page.
TAGRISSO™ (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14) in full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor or, in the absence of tumor, plasma specimens prior to initiation of treatment with TAGRISSO [see Indications and Usage (1) and Clinical Studies (14) in full Prescribing Information]. Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food. If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink. If administration via naso-gastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water fluxes (approximately 30 mL).

Dosage Modification

Adverse Reactions

Table 1 Recommended Dose Modifications for TAGRISSO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Interstitial lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td></td>
<td>QTc† interval greater than 500 msec on at least 2 separate ECGs</td>
<td>Withhold TAGRISSO until QTc interval is less than 481 msec or discovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg daily.</td>
</tr>
<tr>
<td>Cardiac</td>
<td>QTc interval prolongation with signs/symptoms of life-threatening arrhythmia</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic, absolute decrease in LVEF of 10% from baseline and below 50%</td>
<td>Withhold TAGRISSO for up to 4 weeks; • If improved to baseline LVEF, resume. • If not improved to baseline, permanently discontinue.</td>
</tr>
<tr>
<td></td>
<td>Symptomatic congestive heart failure</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Other</td>
<td>Grade 3 or higher adverse reaction</td>
<td>Withhold TAGRISSO for up to 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>If improvement to Grade 0-2 within 3 weeks</td>
<td>Resume at 80 mg or 40 mg daily.</td>
</tr>
<tr>
<td></td>
<td>If no improvement within 3 weeks</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when coadministering with a strong CYP3A4 inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer [See Drug Interactions (7), and Clinical Pharmacology (12.3) in full Prescribing Information].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Intestinal Lung Disease/Pneumonitis

Across clinical trials, intestinal lung disease (ILD)/pneumonitis occurred in 3.3% (n=27) of TAGRISSO-treated patients (n=813); 0.5% (n=4) were fatal. Withhold TAGRISSO and promptly investigate in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed [see Dosage and Administration (2.4) and Adverse Reactions (6) in full Prescribing Information].

QTc Interval Prolongation

The heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 411 patients in Study 1 and Study 2, one patient (0.2%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec [see Clinical Pharmacology (12.2) in full Prescribing Information]. In Study 1 and 2, patients with baseline QTc of 470 msec or greater were excluded. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, cosegregation of haplotypes known to prolong the QT interval, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4) in full Prescribing Information].

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, pulmonary edema, ejection fraction decreased or stress cardiomyopathy) occurred in 1.4% (n=11) of TAGRISSO-treated patients (n=813); 0.2% (n=2) were fatal. In Study 1 and Study 2, Left Ventricular Ejection Fraction (LVEF) decline <10% and a drop to <50% occurred in 2.4% (9/375) of patients who had baseline and at least one follow-up LVEF assessment. Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAGRISSO and then at 3 month intervals while on treatment. Withhold treatment with TAGRISSO if LVEF fraction decrease by 10% from pretreatment values and is less than 50%. If symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO [see Dosage and Administration (2.4) in full Prescribing Information].

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level.

Advising pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.3) in full Prescribing Information].

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions (5.1) in full Prescribing Information]

QTc Interval Prolongation [see Warnings and Precautions (5.2) in full Prescribing Information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below reflect exposure to TAGRISSO (80 mg daily) in 411 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy, in two single-arm studies, Study 1 and 2. Patients with a past medical history of ILD or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 ms were excluded from Study 1 and Study 2. Baseline patient and disease characteristics were: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%), metastatic (96%), sites of metastasis (brain metastases (39%), World Health Organization (WHO) performance status of 0 (37%) or 1 (39%), prior line of therapy (EGFR-TKI treatment only, second line, chemotherapy-naïve (31%)), 2 or more prior lines of therapy (69%). Of the 411 patients, 333 patients were exposed to TAGRISSO for at least 6 months; 97 patients were exposed for at least 9 months; however, no patient was exposed to TAGRISSO for 12 months.

In Studies 1 and 2, the most common (>20%) adverse reactions (all grades) observed in TAGRISSO-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Dose reductions occurred in 4.4% of patients treated with TAGRISSO. The most frequent adverse reactions that led to dose reductions or interruptions were: electrocardiogram QTc prolonged (2.2%) and neutropenia (1.9%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. There were 4 patient fatal adverse reactions of TAGRISSO who developed fatal adverse reactions of ILD/pneumonitis. Other fatal adverse reactions occurring in more than 1 patient included pneumonia (4 patients) and CVA/cerebral hemorrhage (2 patients). Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with TAGRISSO. These most frequent adverse reactions that led to discontinuation were ILD/pneumonitis and cerebrovascular accidents/infarctions.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in TAGRISSO-treated patients.
Coadministering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib, compared to administering TAGRISSO alone [see Clinical Pharmacology (12.3) in full Prescribing Information]. Increased BCRP substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP substrate (e.g., rosuvastatin, sulfasalazine, topotecan), unless otherwise instructed in its approved labeling, when coadministered with TAGRISSO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended human dose [see Data]. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 18) at doses of 1 mg/kg/day and above (0.1-times the AUC observed in patients at the recommended dose of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib in human milk. The effects of osimertinib on the breastfed infant or on milk production are unknown. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [see Use in Specific Populations (8.1) in full Prescribing Information]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [see Use in Specific Populations (8.1) in full Prescribing Information].

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO [see Nonclinical Toxicology (12.1) in full Prescribing Information].

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible [see Nonclinical Toxicology (12.1) in full Prescribing Information].

Pediatric Use

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

Geriatric Use

One hundred eighty-seven (45%) of the 411 patients in clinical trials of TAGRISSO were 65 years of age and older, and 54 patients (13%) were 75 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modifications for adverse reactions (23% versus 17%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with mild [creatinine clearance (ClCr) 60-89 mL/min, as estimated by the Cockcroft Gault method (C-G)] or moderate (ClCr 30-59 mL/min, as estimated by C-G) renal impairment. There is no recommended dose of TAGRISSO for patients with severe renal impairment [ClCr <30 mL/min] or end-stage renal disease [see Clinical Pharmacology (12.3) in full Prescribing Information].

Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST). There is no recommended dose of TAGRISSO for patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].

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Welcome to our spring issue of the Magellan Rx™ Report! Each year those who work in the field of managed care pharmacy can expect to face numerous challenges as a result of the Food and Drug Administration (FDA) approval of new chemical entities or new formulations of existing drugs, the launch of generic or biosimilar formulations, and increases in the prices of prescription drugs. For many of us, these challenges are what make managed care such an exciting field to work in; however, these same challenges are what complicate our jobs immensely and make it that much more important to stay ahead of the curve.

At Magellan Rx Management, we help our clients remain at the forefront of the ever-changing world of managed care by developing and executing value-driven solutions, including targeted clinical programs, predictive modeling, and medical pharmacy management. In this issue of the Magellan Rx™ Report, we are excited to share our suggestions for potential formulary policies and medical pharmacy management strategies, as well as updates on various disease states which are likely to impact your organization’s budget now and in the near future.

The feature article of the Magellan Rx™ Report sheds light on gaps in care for patients with non-small cell lung cancer (NSCLC) and identifies opportunities to address these gaps by improving the identification of patients with specific mutations and incorporating mutation test results in the treatment decision-making process.

A second article of focus discusses the availability of numerous injectable, anti-inflammatory therapies available for the treatment of inflammatory conditions and explores the potential role of indication-based formularies in this space. Many of these injectable therapies are indicated for use in multiple inflammatory conditions, such as rheumatoid arthritis (RA) and Crohn’s disease. The majority of payors have implemented preferred product management strategies, with “one of one” or “one of two” approaches comprising these strategies. This article presents an opportunity for payors to analyze medical and pharmacy data to evaluate the potential economic benefits associated with an indication-based formulary.

Another article of interest highlights the high cost associated with intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) treatment and the seemingly limited opportunities available for cost containment. In this article, we discuss the potential benefits, drawbacks, and policy changes required to implement a site of care (SOC) program that aims to reduce overall treatment costs without compromising the quality of care provided to patients. These types of programs have recently gained traction among a limited number of payors, particularly in the infused therapy space, but have not undergone widespread implementation and may represent an underexplored cost savings opportunity that we encourage you to consider.

The final article provides an overview of the current type 2 diabetes mellitus (T2DM) treatment landscape which has undergone a number of changes in the past few months and the high costs of newer, injectable therapies have transitioned this category into a specialty drug category. In this issue, you will also find a summary of various innovative programs that are being implemented by payors across the country. No issue of the Report would be complete without a pharmaceutical pipeline review to help you track promising new agents that may receive FDA approval in the near future.

To learn more about Magellan Rx Management, supporting the initiatives of payors of the future, please feel free to contact us at MagellanRxReport@magellanhealth.com. As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

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Stay on top of managed care trends and become a Magellan Rx Report subscriber. Email us at MagellanRxReport@magellanhealth.com to subscribe today. Magellan Rx Report provides pharmacy and medical management solutions for managed care executives and clinicians. We hope you enjoy the issue—thank you for reading.
Horizon Blue Cross Blue Shield of New Jersey Announces Crohn’s Disease Episode of Care Program

Horizon Blue Cross Blue Shield of New Jersey (Horizon BCBSNJ) and Digestive HealthCare Center, which previously collaborated to establish the first colonoscopy episode of care program in New Jersey, have announced a new partnership to begin a pilot program for Crohn’s disease. The pilot program is a one-year episode of care program that will include approximately 50 Horizon BCBSNJ members and will be conducted by the physicians at Digestive HealthCare across three office locations.

This episode of care program will involve collaboration between Digestive HealthCare and Horizon BCBSNJ’s behavioral health professionals with the goal of identifying Horizon BCBSNJ members who may benefit from behavioral health support and ensuring that these members receive those services. The new program will integrate a mental health assessment and treatment component into the treatment plans of Horizon BCBSNJ members who have Crohn’s disease. The program is designed to create a fully integrated approach to the management of Crohn’s disease and achieve optimal health outcomes for patients with the disease.

Horizon BCBSNJ Episodes of Care Director, Lili Brillstein, commented that patients with chronic diseases may experience behavioral health symptoms which have the potential to negatively impact their physical well-being and medical treatment. Brillstein noted, “Bringing a behavioral health component into this episode can help us understand how to improve care for the whole person which can ultimately enhance the patient experience, improve patient outcomes, and reduce costs.”

This new program will add to Horizon BCBSNJ’s comprehensive list of patient-centered programs, which include Accountable Care Organizations, Patient-Centered Medical Homes, and other Episode of Care programs.


Behavioral Health Home Plus Model Developed by BHARP and UPMC’s Community Care Receives Recognition by SAMHSA’s Program to Achieve Wellness

Community Care Behavioral Health Organization, in partnership with the Behavioral Health Alliance of Rural Pennsylvania (BHARP), developed the Behavioral Health Home Plus model which engages individuals with serious mental illness in addressing their physical health and wellness. The model accomplishes this by helping patients’ behavioral health providers to identify and address their physical health challenges and enabling patients to become more informed and more effective managers of their own overall health. Through this model, Service Coordinators/Case Managers and Certified Peer Specialists incorporate wellness coaching into their role, with a Wellness Nurse joining the behavioral health care provider team and acting as a lead health navigator and consultant.

In 2013, Community Care, the UPMC Center for High-Value Health Care, BHARP, and other stakeholders received the three-year “Optimizing Behavioral Health Homes by Focusing on Outcomes that Matter Most for Adults with Serious Mental Illness” award from the Patient-Centered Outcomes Research Institute (PCORI). The study explores the impact of the model on patient-centered outcomes and uses a comparative effectiveness design to assess the impact of the addition of a wellness nurse to the health home team and the incorporation of self-management tools and strategies to support patients. Although full study results are not yet available, interim results suggest that patients who engaged in the model have reduced their medications for diabetes after achieving significant weight loss, have reported increased energy and health, many have successfully accomplished smoking cessation, and others have reported a reduced severity of their mental health condition as a result of improved physical health.

Community Care, which is part of UPMC, and BHARP announced that their model was acknowledged by Substance Abuse and Mental Health Services Administration’s (SAMHSA) Program to Achieve Wellness for exemplary wellness efforts and received the 2016 Recognition of Excellence in Wellness. SAMHSA’s selection panel determined that the model was exemplary in innovation, replicability, and impact, creating meaningful improvements in the lives of patients in recovery from mental and/or substance use disorders. Full study results are anticipated to be available in spring 2017.

The management of chronic conditions, such as diabetes, typically involves the use of non-pharmacological and pharmacological approaches that target the underlying cause of the disease and aim to control the associated symptoms. More recently, however, it has been discovered that many patients with chronic medical conditions also have comorbid behavioral health conditions, and that the presence of a behavioral health disorder may be a risk factor for developing a chronic condition or vice versa.\(^1,2\) A 2006 study reported that among patients with cancer, 39.8% of patients had comorbid depression/anxiety, and only 5.7% of patients received treatment for this comorbid behavioral health condition.\(^1,3\) Additionally, among patients with diabetes, 30.8% of patients had comorbid depression/anxiety, with only 5.2% of patients receiving treatment for their behavioral health condition.\(^1,3\) In this same study, high rates of comorbid depression/anxiety and low rates of treatment for these conditions were also observed among patients with arthritis, hypertension, chronic pain, asthma, and coronary artery disease.\(^1,3\) The results of this study highlight the opportunity for improved delivery of behavioral health services to patients with chronic conditions and comorbid behavioral health disorders.

The management of this patient population is complex and involves prioritization of treatment, coordination of care, and close monitoring of polypharmacy factors, as this patient population is likely to receive treatment for both conditions simultaneously.\(^1\) As a leader in behavioral health solutions for over 40 years, Magellan offers integrated medical and behavioral health solutions designed to improve outcomes for patients with a wide variety of behavioral health needs. With validated solutions to improve outcomes in patients suffering from the most complex and costly behavioral health conditions, Magellan has the experience to help address this gap in care and improve health outcomes for patients with these conditions.

### REFERENCES

Non-Small Cell Lung Cancer: Opportunities to Improve Gaps in Care

Smoking tobacco remains the leading risk factor for developing lung cancer. Other risk factors include exposure to radon, asbestos, secondhand smoke, and other carcinogens, as well as air pollution, personal or family history of lung cancer, previous lung radiation therapy, and consumption of certain dietary supplements. In addition to risk factors which increase the risk for developing lung cancer, genetic mutations, whether inherited or acquired, may also cause lung cancer.

Approximately 415,000 individuals in the United States have been diagnosed and are living with lung cancer and it has been estimated that there will be 222,500 new cases of lung cancer diagnosed in 2017. Of note, the National Institutes of Health reported that lung cancer resulted in an estimated $13.4 billion in cancer care costs in 2015, excluding costs associated with lost productivity due to death.

Although certain types of lung cancer can be found by screening, few cases are detected with screening, and the majority of cases are diagnosed in advanced stages of disease. Methods used for screening and diagnosis involve imaging tests, including chest x-rays, computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and bone scans. Lung cancer diagnostic tests generally include sputum cytology, thoracentesis, needle biopsy, and bronchoscopy.

A diagnosis of lung cancer can be classified as one of three primary types: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumors. The most common type of lung cancer, NSCLC, represents approximately 80 to 85% of lung cancers, whereas SCLC and lung carcinoid tumors represent 10 to 15% and 5% of lung cancers, respectively (Figure 1). The three most common subtypes of NSCLC include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Each of the subtypes of NSCLC can be further categorized at the molecular level by driver mutations which include AKT1, ALK, BRAF, EGFR, HER2, KRAS, MEK1, NRAS, PIK3CA, RET, and ROS1, along with other mutations.

One of the most common NSCLC mutations is the EGFR mutation which accounts for 10 to 35% of NSCLC mutations. The presence of specific mutations is associated with various clinical parameters and responses to conventional and targeted chemotherapy. Activating EGFR mutations are
associated with high response rates to EGFR tyrosine kinase inhibitor (TKI) therapy and are therefore considered EGFR TKI sensitive mutations. These EGFR mutations include G719X on exon 18, a deletion or insertion on exon 19, and L858R and L861Q on exon 21. However, an insertion mutation on exon 20, specifically the T790M mutation, results in EGFR TKI resistance, thereby resulting in low or non-existent response rates to EGFR TKI therapies. Although the T790M mutation can occur de novo (i.e., inherited), acquired mutations following treatment with EGFR TKI therapies are more common. The most commonly acquired EGFR mutations include exon 19 deletions, the L858R mutation, and the T790M mutation. Of note, the T790M mutation was present in approximately 60% of TKI resistance cases.

The 5-year overall survival (OS) rate for patients with metastatic or stage IV NSCLC is approximately 1%. Additionally, the median OS for patients post-TKI resistance (i.e., development of the T790M mutation) is only 2 years. Fortunately, recent treatment advances have presented this patient population with more targeted treatment options that are designed to block the growth of EGFR T790M-positive tumors. Despite these treatment advances, T790M mutation testing rates may be suboptimal for patients who experience disease progression following treatment with an EGFR TKI and are not candidates for tumor biopsies or have insufficient tumor tissue, resulting in missed or delayed opportunities to identify patients who may benefit from these newer treatment options. These low testing rates suggest that areas of improvement may exist. Interventions to consider include patient and provider education surrounding the availability of newer, less invasive mutation testing options which may help guide providers in the treatment selection process for patients who have failed initial treatment options.

**Treatment Landscape**

The European Society for Medical Oncology (ESMO) has published clinical practice guidelines for the diagnosis, treatment, and follow-up of stage IV, metastatic NSCLC, the most advanced stage of lung cancer. These guidelines recommend establishing histological subtype (i.e., adenocarcinoma, large cell cancer, NSCLC not otherwise specified, or squamous cell carcinoma) and using minimal immunohistochemistry (IHC). Of note, the guidelines recommend avoiding excessive, unnecessary IHC as it will consume tumor tissue and has the potential to prevent subsequent molecular analysis. Additionally, the ESMO guidelines note the importance of obtaining adequate tissue material for histological diagnosis and molecular testing for the purpose of individualizing treatment options.

On progression, tumor re-biopsy should be considered and is recommended in patient subgroups where re-testing has the potential to guide subsequent treatment. Driver mutations (e.g. EGFR, ALK, etc.) have been identified in NSCLC and there are Food and Drug Administration (FDA)-approved targeted treatments for some of these mutations, but not all, which highlights the importance of identifying the presence of mutations for which targeted treatments are currently available. Given that activating EGFR mutations are predictive of response to TKI therapy, it is important to identify the presence of the EGFR mutation in this patient population because these treatments offer an improved response rate, progression free survival, and quality of life and better tolerability compared to platinum-based chemotherapy in the first-line setting.

The ESMO guidelines note that EGFR mutation testing is recommended in all patients with advanced NSCLC, but not recommended in patients with an unequivocal diagnosis of SCLC, except in never/former light smokers (<15 pack years). These guidelines specifically recommend using a testing methodology that provides the test sensitivity required for the sample’s tumor content and provides adequate coverage of all clinically relevant mutations, including mutations in exons 18-21, and especially those associated with specific drug resistance. Further, the guidelines note that at a minimum, the most...
common activating mutations, exon 19 deletion and exon 21 L858R point mutation, including exon 20 T790M, should be determined.\textsuperscript{15}

Treatment selection for patients with advanced/metastatic disease depends on histology, molecular pathology, performance status, comorbidities, and patient preferences.\textsuperscript{15} For patients with stage IV, EGFR-mutated disease, first-line treatment options include gefitinib, erlotinib, and afatinib.\textsuperscript{15} Unfortunately, the majority of patients will progress after 9 to 12 months of treatment with an EGFR TKI and the most common mechanism of acquired resistance is the development of the T790M mutation.\textsuperscript{15} Patients whose disease progresses following EGFR TKI treatment should undergo a re-biopsy to perform a molecular analysis to identify the presence or absence of the EGFR T790M mutation.\textsuperscript{15} For patients who are not candidates for tissue re-biopsy, validated liquid biopsies represent an alternative testing modality.\textsuperscript{15} Currently, the only FDA-approved treatment for patients with metastatic EGFR T790M mutation-positive tumors is osimertinib (Tagrisso\textsuperscript{®}, AstraZeneca).\textsuperscript{15}

**Mutational Analysis Testing and Gaps in Care**

The selection of targeted therapies should be guided by the presence of driver mutations. Presently, targeted treatment options are available for the ALK, EGFR, and ROS1 mutations in NSCLC.\textsuperscript{8} Ongoing research is being conducted to develop targeted treatment options for mutations for which targeted treatment options do not currently exist. Given that the EGFR mutation occurs in NSCLC patients at a greater frequency than ALK or ROS1 combined, the focus of this article will be on the EGFR mutation and the current gaps in care that exist for this patient population.

According to treatment guidelines, DNA mutational analysis is the preferred method for assessing EGFR status. Data from a real-world survey indicate that mutational analysis testing rates among this population are suboptimal, with approximately 76% of newly diagnosed patients in North America undergoing testing to assess EGFR status.\textsuperscript{16} Unknown EGFR mutational status at the time of initial treatment selection is not uncommon, as many patients begin NSCLC treatment prior to the availability of mutation test results due to the urgency to treat; however, the unavailability of mutation test results throughout the entirety of the disease management course creates the potential for patients to continue to receive ineffective or suboptimal treatment, thereby negatively affecting patient outcomes and resulting in treatment waste.\textsuperscript{14,17}

Until recently, the only option for assessing EGFR mutational status via DNA mutational analysis was by tissue biopsy sequencing, which is considered the gold standard; however, tissue biopsies are invasive procedures and research has indicated that approximately 30% of patients with lung cancer may have insufficient biopsy tissue or are not candidates for a tumor biopsy.\textsuperscript{14} Of note, lung biopsies are commonly performed at the time of diagnosis. Additionally, it is extremely rare for a patient to inherit the T790M mutation because it is an acquired mutation that appears following resistance to first-line TKI therapy. Therefore, it is unlikely that the original tissue sample from the initial biopsy will contain the T790M mutation. As such, until the recent approval of an alternative mutational analysis test, the identification of patients who had EGFR T790M-positive tumors would have required performing an additional lung biopsy.

The Cancer Moonshot Task Force has identified several unmet needs in cancer care, including the need for non-invasive tests for markers to hasten the process in detecting the emergence of drug-resistant disease.\textsuperscript{18,19} To address this unmet need, several companies have begun the development of non-invasive tests, including plasma- and urine-based biopsies. While some companies have begun to launch such tests, not all tests have received FDA approval. The FDA recently approved cobas\textsuperscript{®} EGFR Mutation Test v2, the first plasma-based, real-time, polymerase chain reaction (PCR) test indicated for the qualitative detection of defined mutations in the EGFR gene, including T790M, in NSCLC patients from whom a tumor biopsy cannot be obtained.\textsuperscript{20} This plasma-based test utilizes circulating cell-free DNA (cfDNA) from the plasma derived from ethylenediaminetetraacetic acid (EDTA) anti-coagulated peripheral whole blood.\textsuperscript{20} A number of other manufacturers currently offer cfDNA platforms to detect EGFR T790M resistance mutations; however, such tests have not yet received FDA approval. Of note, circulating tumor DNA (ctDNA) platforms are available as well.

One of the major differences between tissue-, plasma-, and urine-based biopsies is the process by which the cells are acquired. Tissue biopsies involve surgical procedures to extract adequate tumor tissue which can subsequently be tested on a wide variety of platforms.\textsuperscript{21} Plasma-based testing involves blood draws which extract cfDNA or ctDNA shed by the tumor and urine-based testing utilizes ctDNA present in urine as an alternative testing modality.\textsuperscript{22} Another notable difference among the various testing options is the

**“Despite these treatment advances, T790M mutation testing rates may be suboptimal for patients who experience disease progression following treatment with an EGFR TKI.”**
analytic sensitivity which can vary greatly depending on whether tissue, plasma, or urine is utilized. A pooled analysis indicated that the recently FDA-approved plasma-based cfDNA test has a sensitivity of 70 to 80%, indicating that the test can have false negatives, and a high level of specificity ranging from 90 to 100%. When utilizing the tissue biopsy results as a reference, the sensitivity of the urine-based EGFR T790M mutation test is similar to that of the plasma-based test, ranging from 70 to 80%. Of note, various testing platforms are available across a wide variety of companies and testing centers, and sensitivities may be lower or higher depending on which platform is used. Therefore, it remains important that any mutational analysis testing platforms that are currently in the stages of development or have already launched must be validated against an acceptable reference in order to ensure that the test results are accurate.

Although the analytic sensitivities of the plasma- and urine-based tests are lower than that of the gold standard, the tissue-based test is not without flaw and there is the potential that the T790M mutation, although present in the plasma, may not appear in the biopsy-extracted tumor tissue, leading providers and patients to believe that a patient may have the T790M-negative form of disease when the patient is T790M-positive. Tumor biopsies are also more costly than alternative testing options, with a mean cost of $14,634 for each tissue biopsy and costs between $1,000 and $5,000 for plasma assays. Additionally, tumor biopsies have longer turnaround times. A recent study indicated that the median turnaround time for liquid biopsies is 3 days compared to 12 days for tissue biopsies performed in newly diagnosed patients and 27 days for patients with the drug resistant form of disease.

Potential Solutions to Improve Quality of Care and Implications for Payors

The increasing availability of newly FDA-approved and Clinical Laboratory Improvement Amendments (CLIA)-approved testing options presents patients and providers with attractive alternative testing modalities that may be less invasive, less costly, and offer faster turnaround times compared to tissue biopsies. Despite the availability of these new mutational analysis testing options, the level of coverage for these tests is not standard across the payer landscape, with some payors providing coverage and others restricting coverage until the analytic sensitivity of the tests increases to a rate that is deemed acceptable. Of note, even payors that provide coverage for these new testing alternatives may be offering a reimbursement rate that hinders providers from utilizing such tests in the disease management course for their patients. Payors should review their companion diagnostic coverage policies and reimbursement contracts to determine whether coverage should be expanded or remain the same until improved sensitivity testing options become available and/or revisit their reimbursement contracts to ensure providers are compensated appropriately for the new mutation testing options.

It may also be beneficial for payors to identify members who may not be candidates for tumor biopsies to ensure that these patients have access to an alternative mutation testing option upon disease progression. The identification of members may involve the implementation of a disease management program for members for whom a diagnosis of lung cancer has been identified but for whom there are no claims for mutation testing of any type. With this program setup, there is the potential that members may have previously undergone a mutational analysis prior to enrollment in their current plan or that the data may capture patients who have not yet experienced disease progression on their current treatment; however, the potential benefits that could be derived by identifying patients who could benefit from mutational analysis testing but have not had such testing done may justify the time and effort required to conduct this type of program.

Future Directions

Despite the fact that the EGFR mutation represents one of the most common mutations among patients with NSCLC and that nearly 60% of patients with this mutation will develop the T790M mutation following treatment with a TKI, the number of patients with this mutated form of disease is small. Although the patient population is small, these patients have an actionable driver mutation for which a targeted treatment option exists once disease progression occurs. Identifying patients who may benefit from this treatment can reduce treatment waste by preventing the continued treatment with an ineffective agent once disease progression occurs and potentially improve patient outcomes by offering patients a targeted treatment that may result in tumor shrinkage and a median duration of response of one year. The identification of these patients may require revisions to existing coverage options.

“Tissue biopsies are invasive procedures and research has indicated that approximately 30% of patients with lung cancer may have insufficient biopsy tissue or are not candidates for a tumor biopsy.”
policies for companion diagnostics in order to expand access to less invasive mutation testing options for patients who are not candidates for tumor biopsies.

While liquid biopsies do not currently present an opportunity to completely eliminate tumor biopsies, their availability offers an alternative, less invasive testing option for patients with metastatic disease who are not candidates for tissue biopsies. With improved analytic sensitivity of these tests, liquid biopsies may someday offer a first-line mutation testing alternative to tumor biopsies in patients who have already undergone a tumor biopsy at diagnosis and have progressed on first-line therapy.

**REFERENCES**

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Although not universally classified as autoimmune diseases, there are other chronic conditions, such as ulcerative colitis (UC) and Crohn’s disease (CD), that are considered autoimmune related diseases. UC and CD are also characterized by inflammation and utilize many of the same pharmacological treatments in their management.

The management of autoimmune diseases and autoimmune related diseases is extremely costly due to the chronic nature of these diseases, their responsiveness to pharmacological therapies, and their widespread impact, with an estimated 50 million Americans affected. Based on an estimate from the National Institutes of Allergy and Infectious Diseases (NIAID), annual direct health care costs of autoimmune diseases in the United States exceed $100 billion. The American Autoimmune Related Diseases Association (AARDA) has suggested that the true costs of treating autoimmune disease may actually be much higher given that the annual treatment cost of only 7 of more than 100 autoimmune diseases ranges from $51.8 to $70.6 billion. Of note, PsO, RA, UC, and CD represent 4 of the 7 autoimmune diseases and autoimmune related conditions included in this estimate. Due to their shared characteristic of inflammation, these conditions will herein collectively be referred to as inflammatory conditions.

The treatment of inflammatory conditions primarily involves the use of anti-inflammatory drugs which may include older, traditional therapies as well as newer, injectable therapies, which are commonly referred to as biologics (Table 1). The annual cost of treatment with commonly used biologic agents is within the range of approximately $20,000 to $30,000 per year for commercially insured patients. It is important to note that patient cost sharing, which likely ranges from hundreds to thousands of dollars each year, will vary based on any copay and/or coinsurance responsibilities and any applicable deductibles. In addition to direct medical costs to the health care system and patients, inflammatory diseases are also associated with large indirect costs, such as those associated with lost productivity and disease-related disability, and...
these indirect costs vary based on the specific inflammatory disease.3

Due to the high costs associated with biologic treatments, many payors have begun to explore a variety of management strategies with the objective of providing coverage of appropriate treatment options while managing treatment-associated costs. Such management strategies have included step therapy requirements hinging upon one or more trials with corticosteroids, disease modifying antirheumatic drugs (DMARDs), topical therapies, or suppositories, depending on the inflammatory condition; selecting preferred anti-inflammatory products; and more recently, exploring the impact of indication-based formularies on treatment-related costs. Each management strategy has benefits and drawbacks that should be carefully considered before being implemented at the payor level and this article seeks to highlight these important, payor-directed considerations.

**Treatment Landscape**

Treatment guidelines for PsO, RA, and UC/CD are published by the American Academy of Dermatology (AAD), American College of Rheumatology (ACR), and the American College of Gastroenterology (ACG)/the American Gastroenterological Association (AGA), respectively. Of note, the ACG UC treatment guidelines and the AGA CD guidelines were last updated in 2010 and 2013, respectively; however, the AGA has also published clinical care pathways for the management of UC and CD in 2015 and 2014, respectively, and these pathways offer a more up-to-date resource for clinicians. Treatment selection for these conditions is guided by symptom severity, disease stage (early vs late stage), and previous trials of pharmacological agents, when applicable.

The management of PsO typically involves phototherapy, photochemotherapy, topical therapy, systemic agents, and biologics.6 Topical therapy regimens utilize corticosteroids, vitamin D analogs, tazarotene, tacrolimus, pimecrolimus, emollients, salicylic acid, anthralin, and coal tar.6 Systemic therapies include methotrexate (MTX), cyclosporine, retinoids, azathioprine (AZA), hydroxyurea, leflunomide, mycophenolate mofetil (MMF), sulfasalazine (SSZ), and tacrolimus.6 Biologic treatments used in the management of PsO include the following tumor necrosis factor (TNF) inhibitors: adalimumab (Humira®, AbbVie, Inc.), etanercept (Enbrel®, Amgen), and infliximab (Remicade®, Janssen).6 For limited disease, targeted phototherapy or topical therapies are recommended.6 If these strategies are ineffective, or if a patient has extensive disease, phototherapy/photochemotherapy, systemic, or biologic treatments may be used.6 The AAD treatment guidelines were last updated in 2008 and thus do not include a recommendation regarding the recently Food and Drug Administration (FDA)-approved treatment, ixekizumab (Taltz®, Eli Lilly and Company), which is indicated for the treatment of adults with moderate to severe PsO who may benefit from taking injections or systemic therapies or phototherapy.7

The ACR treatment guidelines for RA are more complex and include recommendations for the treatment of patients with early RA (disease duration < 6 months) and established RA (disease duration ≥ 6 months).8 For patients with symptomatic, early RA, ACR recommends using a treat-to-target strategy.8 If disease activity is low in DMARD-naïve patients, DMARD monotherapy (MTX preferred) is recommended over a TNF; however, if disease activity is moderate or high in DMARD-naïve patients, DMARD monotherapy (MTX preferred) is preferred over either tofacitinib or combination DMARD therapy.8 In patients whose disease activity remains moderate or high despite DMARD monotherapy, recommendations include combination traditional DMARDs or the addition of a TNF or a non-TNF biologic or tofacitinib.9 Such recommendations are preferred over the continuation of DMARD monotherapy.8 In patients whose disease activity remains moderate or high despite TNF therapy and who are not currently receiving DMARD therapy, ACR recommends the addition of one or two DMARDs to TNF therapy over the continuation of TNF therapy alone.8 If disease activity is low, ACR recommends the continuation of DMARD therapy or continuation of TNF, non-TNF biologic, or tofacitinib over the discontinuation of each respective medication.8

As mentioned previously, the ACG UC treatment guideline was last updated in 2010, and therefore does not include recommendations for treatments that received FDA approval after its publication. In 2015, the AGA released a clinical care pathway for the treatment of UC.3 The AGA clinical care pathway notes that following diagnosis and assessment of inflammatory status, patients should be stratified according to colectomy risk.9 For low-risk patients, recommendations
for induction therapy include oral 5-aminosalicylic acid (5-ASA) and/or rectal 5-ASA and/or oral budesonide or prednisone and/or rectal steroids, and note that rectal 5-ASA is first-line therapy in distal UC. If remission is achieved, recommendations for maintenance therapy include oral 5-ASA and/or rectal 5-ASA and tapering of steroids over 60 days. If remission is not achieved, or if patients experience relapse following remission with maintenance therapy, the pathway suggests utilizing the recommended inductive and maintenance therapies for the high-risk outpatient which are discussed below.

For high-risk patients, those requiring hospitalization should be identified, and treatment recommendations depend on whether the patient is in the outpatient or inpatient setting. In the outpatient setting, one recommendation for induction therapy is a short course of steroids with initiation of a thiopurine, and if remission is achieved, treatment options include a thiopurine plus tapering of steroids over 60 days, or an anti-TNF (i.e., TNFI) with or without a thiopurine, or vedolizumab with or without a thiopurine or MTX. Two additional recommendations include induction and maintenance treatment with an anti-TNF agent with or without a thiopurine or vedolizumab with or without an immunomodulator. Of note, combination therapy with a thiopurine is more efficacious than anti-TNF monotherapy and thus, should be considered, especially in patients who have failed at least one anti-TNF therapy. If remission is not achieved or if patients experience relapse, the pathway suggests utilizing the recommended therapies for the high-risk outpatient not in remission, which are discussed below.

For high-risk outpatients not in remission, treatment recommendations depend on a patient’s response to previous therapies. For patients who fail to respond to prednisone, treatment recommendations include an anti-TNF agent with or without a thiopurine or vedolizumab with or without an immunomodulator. If a patient fails to maintain steroid-induced remission on a thiopurine and has subtherapeutic 6-thioguanine nucleotide (6TGN) levels, the dose should be increased and metabolites should be rechecked; however, the recommendation for patients with therapeutic 6TGN levels is to switch to an anti-TNF agent or vedolizumab. If there is a loss of response to an anti-TNF agent, recommendations for a subtherapeutic level/no or low antibodies include increasing the dose and/or decreasing intervals as well as the addition of an immunomodulator; for a subtherapeutic level/high antibodies, a switch within class; for a therapeutic level, a switch to vedolizumab with or without an immunomodulator. If patients experience a loss of response to vedolizumab, the dose should be increased to 300 mg every 4 weeks, or if patients are non-responders, the recommendation is to switch to an anti-TNF agent with or without a thiopurine. Treatment recommendations for high-risk inpatients are beyond the scope of this article and therefore will not be discussed.

Both the ACG and AGA have published treatment guidelines for CD; however, these guidelines were last updated in 2009 and 2013, respectively. In 2014, the AGA released a clinical care pathway for the management of CD. Following assessment of inflammatory status, comorbidities and disease- and therapy-related complications, and current and prior disease burdens, clinicians should identify patients as being low-risk or moderate/high-risk. Initial treatment options for low-risk patients with involvement of the ileum and/or proximal colon and minimal to no systemic symptoms include treatment with budesonide with or without AZA or tapering a course of prednisone with or without AZA. For diffuse or left colon involvement with minimal to no systemic symptoms, a tapering course of prednisone with or without AZA is recommended. In moderate/high-risk patients with moderately severe CD, options include anti-TNF monotherapy over either no therapy or thiopurine monotherapy, anti-TNF plus thiopurine over either thiopurine monotherapy or anti-TNF monotherapy, and MTX for patients who do not tolerate a purine analog in combination with anti-TNF. Of note, combination therapy with an immunosuppressant and anti-TNF offers improved efficacy and durability versus anti-TNF monotherapy and should be considered for moderate/high-risk patients who require a second or third biologic.

For low-risk patients in remission, options include stopping therapy and observing, budesonide, or immunosuppressive therapy. For moderate/high-risk patients with steroid-induced remission, options include an immunomodulator over no immunomodulator, or an anti-TNF with or without a thiopurine over no anti-TNF. An anti-TNF with or without a thiopurine is recommended for moderate/high-risk patients with anti-TNF or anti-TNF plus thiopurine induced remission. Recommendations for low-risk patients not in remission include immunosuppressive agents, assessment of drug levels, and consideration of anti-TNF therapy. For moderate/high-risk patients not in remission, options include anti-TNF monotherapy over either no therapy or thiopurine monotherapy, or an anti-TNF therapy plus a thiopurine over either "The annual cost of treatment with commonly used biologic agents is within the range of approximately $20,000 to $30,000 per year for commercially insured patients."
thiopurine monotherapy or anti-TNF monotherapy.10

With regard to treatment with vedolizumab, the FDA-approved labeling specifies that it is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response with, lost response to, or were intolerant to an anti-TNF agent or immunomodulator or who had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.11 Additionally, the labeling mentions that vedolizumab is indicated for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator, or who had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.11

Although the FDA-approved labeling highlights the role of vedolizumab as a second-line therapy for patients with UC and CD, it is important to note that the AGA’s clinical care pathways for UC/CD have identified vedolizumab as a first-line biologic option following

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<th>TABLE 1. PRICING OF BIOLOGICS</th>
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<td>Inflectra® (biosimilar; reference product: Remicade®)</td>
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**Abbreviations:** IV=intravenous, SC=subcutaneous, TNF=tumor necrosis factor, TNFI=tumor necrosis factor inhibitor

**WAC (for brand name product only) as of 2/6/2017**

*Weight-based dosing using patient weight of 70 kg*
treatment failure with traditional agents for these patient groups.9-11

One major change in the anti-inflammatory treatment landscape has been the FDA approval of certain biosimilars, including biosimilars for infliximab (infliximab-dyyb/Inflectra®, Celltrion, Inc./Pfizer Inc.), etanercept (etanercept-szpz/Enbrel®, Pfizer Inc.), or etanercept biosimilars for inflammatory conditions outside of the FDA-approved indication. Product availability, pricing, and utilization are factors that must be taken into consideration before the FDA-approved indication is expanded. The availability of cost-effective alternative treatment options is also a consideration. Moreover, payors and providers must be aware of the development of biosimilars and expanded: indications for traditional and biosimilar agents.

Payors’ Management Strategies
The high costs of treatments, particularly biologics, have prompted payors to implement management strategies that balance access to treatment with managed care. Commonly utilized strategies consist of step therapy requirements, preferred anti-inflammatory products, and indication-based formularies. Step therapy requirements and the selection of preferred products are more basic management strategies that are frequently used in disease states for which there are multiple treatment options with similar efficacy and tolerability profiles within a therapeutic class and generally mirror the step-wise progression of therapy presented in treatment guidelines.

For inflammatory conditions, step therapy requirements have historically mandated that a member has had one or more trials with corticosteroids, DMARDS, topical therapies, and/or suppositories, when applicable, before coverage of a biologic would be provided. These requirements are based on treatment guideline recommendations and the step therapy policies typically encourage the use of less costly agents first, and if treatment failure occurs, subsequent treatment with costlier agents would be considered. Not all patients are candidates for these less costly treatment options and patients and providers tend to view this “fail first” strategy as an unnecessary burden that prevents access to appropriate treatment options.17

Several states have been enacting or have been considering legislation that would protect patients from step therapy policies.17 For example, Connecticut has already passed a bill that prevents payors from requiring that patients have a trial with a less costly treatment option for longer than 60 days.18 Other states have followed suit and many more states have recently enacted step therapy legislation or have pending legislation.18

In addition to implementing step therapy requirements, payors have also selected preferred products within each therapeutic class. The selection of preferred products is often based not only on clinical evidence of efficacy, but also the availability of financial incentives and/or value-added programs. The decision to implement a preferred product strategy for biologics involves acknowledging that not all biologic products are indicated for use in every inflammatory condition, and outside of the FDA-approved labeling, products have varying levels of evidence of efficacy for use in each condition. Therefore, selecting one or two preferred TNFIs and non-TNF biologics may not provide adequate access to appropriate treatments for conditions outside of the aforementioned four inflammatory conditions being highlighted in this discussion. It is crucial that payors ensure that an exception process is incorporated into any policies that are developed so that members who have conditions that do not respond to the preferred products or who have contraindications or intolerances to these products are given access to appropriate, non-preferred treatments.

More recently, payors have begun conducting analyses that demonstrate a potential for cost offsets via an indication-based management approach. Indication-based formularies involve the development of individual formularies for each inflammatory disease and would include only treatments that are indicated for use in a particular inflammatory condition. The development of an indication-based formulary requires a thorough analysis of the nuances of product utilization across both the medical and pharmacy benefits. Due to wide variability in utilization, economic considerations, and other differences, it is imperative that payors perform an in-depth analysis that gives consideration to numerous factors prior to implementing this type of approach. These factors will include, but are not limited to, data issues (e.g., availability, accessibility, etc.), amount of time required to conduct an analysis, the use of medical data for ICD-10 codes vs physician specialty, the potential for patients to have multiple comorbidities, differences in utilization and management capabilities for the medical and pharmacy benefits, and the possibility of encountering patients for whom a condition cannot be confirmed. The magnitude of potential cost offsets will differ for each plan and careful consideration must be given by payors before implementing this type of strategy; however, this innovative formulary management approach is a potential option for some plans.

Future Directions and Conclusion
The introduction of newer biologic therapies, expanded indications for use of already available products, recent approval of three biosimilars
within the anti-inflammatory category, and the recently-implemented or soon-to-come, state-specific legislative changes surrounding payors’ policies have collectively resulted in the need for newer, more creative management strategies. Further changes are expected to occur in this therapeutic category, particularly because of the potential new additions to the market: guselkumab (Janssen), which is being developed for the treatment of moderate to severe PsO, and sirukumab (GlaxoSmithKline, Janssen), which is being studied for the treatment of moderate-to-severely active RA. Of note, brodalumab (SILIQ™) recently received FDA approval in February 2017 for the treatment of patients with moderate to severe PsO in adults who are candidates for systemic therapy or phototherapy. The FDA-approved labeling for the product, which has not yet been launched, will be accompanied by a Boxed Warning because of the risk of suicidal ideation and behavior and will only be available through a Risk Evaluation and Mitigation Strategy (REMS) program. Payors are faced with the challenge of designing management strategies that are geared toward balancing access to treatment with cost containment while also ensuring that these strategies are aligned with any applicable legislative mandates and can quickly be adjusted to incorporate any potential FDA approvals in this space. At this time, it is recommended that payors review their medical and pharmacy claims data to assess any potential economic opportunity that may exist with the implementation of an indication-based formulary in any of these inflammatory disease states and also proactively review the aforementioned pipeline agents, all of which have the potential to receive FDA approval in 2017.

REFERENCES

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Immune Globulin: 
Site of Care Management Program Opportunities

Immune globulin (IG) products have been utilized to treat immunodeficiency since the early 1950s. Since their discovery, the list of uses for IG products has continued to grow, with some indications backed by significant research and real-world experience and others largely considered experimental. Traditionally, IG products have been administered intravenously (IVIG); however, in recent years, newer subcutaneously administered IG (SCIG) products have become available. The large number of products and the even larger number of potential therapeutic indications, with highly variable levels of supporting evidence for use, make this a challenging category for payors to manage. Adding to the complexity of this category, the cost to administer these products varies greatly based on the site of care (SOC) in which the product is delivered. Collectively, these challenges have posed a large dilemma for managed care organizations (MCOs) and have created an urgent need for superior management strategies.

Treatment Landscape:

There are numerous commercially available IG products produced by multiple manufacturers. Products may differ based on a variety of factors including, but not limited to, immunoglobulin A (IgA) content, cost, dosage form and strength, viral inactivation process, storage requirements, route of administration, and Food and Drug Administration (FDA)-approved indication(s). Individual product selection should be determined according to product availability and evidence for use in the selected condition and patient-specific characteristics.

Currently available IVIG products include Bivigam™, Carimune® NF, Flobogamma DIF® (5% and 10%), Gammagard Liquid®, Gammagard S/D® (IgA less than 1 mcg/mL), Gammaked™, Gammaplex®, Gamunex®-C, Octagam®, and Privigen®. Of note, Gammagard® Liquid, Gammaked®, and Gamunex®-C can be administered through both IV and SC routes of administration. Three SC-only products, Cuvitru™, Hizentra®, and HyQvia®, are also commercially available. HyQvia® differs from its SC-only counterparts in that it represents a dual vial unit containing both immunoglobulin G (IgG) and recombinant human hyaluronidase. Additionally, intramuscularly administered IG (IMIG) products are available, which are typically referred to as hyper-immune globulin products; however, these products are generally indicated in a different setting (prophylaxis against infectious diseases and to provide passive immunity to unimmunized or immunosuppressed patients) and thus will not be included in the discussion or tables that follow.

There are notable differences between the two primary routes of ad-
ministration, IV and SC. IV administration permits administration of larger volumes of product compared to SC administration; however, SC formulations are typically more concentrated than IV formulations, thereby reducing the volume needed to administer the desired level of IgG. Additionally, IV administration is typically associated with longer infusion times and potentially more systemic adverse effects compared to SC administration. The frequency of IVIG administration is generally every three to four weeks (i.e., bolus dosing) for immune deficiencies; however, the frequency of administration in inflammatory and autoimmune disorders can vary greatly across all indications. In contrast, SC administration can range from daily (i.e., rapid-push SC) to weekly (i.e., traditional SC) to every-three-to-four weeks administration (i.e., hyalurondase-facilitated SCIG).

There is also a great deal of variation in cost across the wide array of available products. The wholesale acquisition cost (WAC) for each product, excluding any rebates or discounts, is listed in Table 1. A recent medical pharmacy trend report indicated that the annual cost of IVIG per patient in the commercial setting was comparable, with annual costs primarily in the range of $40,000 to $50,000. It is important to note, however, that the dosing and administration of each product is highly variable depending on the condition being treated and therefore the cost listed for the individual products may not necessarily be reflective of the actual cost of treatment. The products also differ according to their FDA-approved indications, including patient age groups in which each treatment is approved, which are detailed in Table 1. Regardless of their FDA-approved labeling, these products are frequently used in the off-label setting based on real-world experience and research conducted outside of FDA-approved clinical trials; however, not all off-label indications have the same level of evidence supporting their use.

Collectively, the FDA-approved indications for currently available IG products include the following:

FDA - Approved Indications for IG Products

**The treatment of primary immunodeficiency diseases (PIDs)**

- Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia (CLL)
- To increase platelet counts in patients with immune thrombocytopenic purpura (ITP) to prevent or control bleeding
- Prevention of coronary artery aneurysms in patients with Kawasaki syndrome
- Maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy (MMN)
- Improvement in neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP)

Although no longer available, Gammagard S/D® had been granted FDA-approval for use in two additional settings: prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation, and reduction of serious bacterial infection in children with pediatric human immunodeficiency virus (HIV-1) infection. Given that this product was discontinued by the manufacturer, payors are left with the decision to either cease or continue coverage of currently available products for these off-label indications.

**Economic Implications and Challenges to Management**

As evidenced by the WAC details listed in Table 1 and by the annual treatment cost per patient noted in the aforementioned medical pharmacy trend report, IG product costs alone largely contribute to the overall treatment cost for patients receiving IG therapy. Of note, the overall treatment cost for this patient population is also greatly impacted by the SOC where the treatment is administered (e.g., hospital vs clinic vs home settings) due to the wide variability in associated administration costs. Payors’ attempts to manage this therapeutic class have included a variety of strategies, such as restricted access to specific IG products (i.e., preferred
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>FDA Approved Indication(s)</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Strength</th>
<th>Package Size</th>
<th>Wholesale Acquisition Cost (WAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma 5% DIF</td>
<td>Grifols Biologicals Inc.</td>
<td>PI (≥2 years of age)</td>
<td>IV</td>
<td>Solution</td>
<td>50 mg/mL</td>
<td>10 mL</td>
<td>$44.12</td>
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<td></td>
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<td>200 mL</td>
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<td></td>
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<td>400 mL</td>
<td>$1,764.51</td>
</tr>
<tr>
<td>Flebogamma 10% DIF</td>
<td>Grifols Biologicals Inc.</td>
<td>PI (≥2 years of age)</td>
<td>IV</td>
<td>Solution</td>
<td>100 mg/mL</td>
<td>50 mL</td>
<td>$441.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mL</td>
<td>$882.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 mL</td>
<td>$1,764.51</td>
</tr>
<tr>
<td>Gammagard Liquid</td>
<td>Baxalta Inc.</td>
<td>PI (≥2 years of age, MMN (adults))</td>
<td>IV, SC</td>
<td>Solution</td>
<td>100 mg/mL</td>
<td>10 mL</td>
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<td></td>
<td>100 mL</td>
<td>$1,306.14</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 mL</td>
<td>$2,612.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mL</td>
<td>$3,918.90</td>
</tr>
<tr>
<td>Gammagard S/D (IgA less than 1 mcg/mL)</td>
<td>Baxalta Inc.</td>
<td>PI (≥2 years of age, B-CLL, ITP (adults), Kawasaki syndrome (pediatrics))</td>
<td>IV</td>
<td>Powder, reconstitutable</td>
<td>5 gm</td>
<td>10 gm</td>
<td>$843.50</td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>10 gm</td>
<td>$1,687.00</td>
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<td>Gammaked</td>
<td>Kedrion Biopharma, Inc.</td>
<td>PI, ITP, CIDP</td>
<td>IV; SC (only PI)</td>
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<td>10 mL</td>
<td>$123.62</td>
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<td></td>
<td>100 mL</td>
<td>$1,236.14</td>
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<td></td>
<td></td>
<td>200 mL</td>
<td>$2,472.27</td>
</tr>
<tr>
<td>Gammaplex</td>
<td>Bio Products Laboratory USA, Inc.</td>
<td>PI (≥2 years of age), ITP</td>
<td>IV</td>
<td>Solution</td>
<td>50 mg/mL</td>
<td>100 mL</td>
<td>$694.15</td>
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<td>200 mL</td>
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<td>400 mL</td>
<td>$2,776.60</td>
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<tr>
<td>Octagam</td>
<td>Octapharma USA, Inc.</td>
<td>ITP (adults)</td>
<td>IV</td>
<td>Solution</td>
<td>50 mg/mL</td>
<td>20 mL</td>
<td>$138.42</td>
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<td>50 mL</td>
<td>$346.05</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>500 mL</td>
<td>$3,460.50</td>
</tr>
<tr>
<td>Octagam 10%</td>
<td>Octapharma USA, Inc.</td>
<td>ITP (adults)</td>
<td>IV</td>
<td>Solution</td>
<td>100 mg/mL</td>
<td>20 mL</td>
<td>$276.84</td>
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<td>$692.10</td>
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<td></td>
<td>100 mL</td>
<td>$1,384.20</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>200 mL</td>
<td>$2,768.40</td>
</tr>
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</table>
patients who have experienced anaphylactic or anaphylactoid reactions following administration of IG products with moderate IgA content. The emergence of such reactions resulted in the development of a product with low IgA content.

As mentioned previously, there are notable differences in the formulations and strengths of the currently available IG products. Some of the differences in formulations include the level of IgA content and sucrose content. The level of IgA content plays a large role in the treatment selection process for patients with renal insufficiency or who are undergoing renal transplantation. Sucrose content in IG products is a point of concern for these patients because many IVIG formulations utilize sucrose as a stabilizer and sucrose can lead to renal tubular injury.

For these patients, a transition from a low-IgA or sucrose-free product to a moderate-IgA or sucrose-containing product, respectively, could result in negative health outcomes. Therefore, it is ex-

### TABLE 1. AVAILABLE IG PRODUCTS

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>FDA Approved Indication(s)</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Strength</th>
<th>Package Size</th>
<th>Wholesale Acquisition Cost (WAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Privigen</td>
<td>CSL Behring LLC</td>
<td>PI, ITP</td>
<td>IV</td>
<td>Solution</td>
<td>10%</td>
<td>50 mL</td>
<td>$660.00</td>
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<td></td>
<td></td>
<td>100 mL</td>
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<td></td>
<td></td>
<td></td>
<td>200 mL</td>
<td>$2,640.00</td>
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<td></td>
<td></td>
<td></td>
<td>400 mL</td>
<td>$5,280.00</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>Grifols Biologicals Inc.</td>
<td>PI, ITP, CIDP</td>
<td>IV, SC</td>
<td>Solution</td>
<td>100 mg/mL</td>
<td>10 mL</td>
<td>$105.51</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>25 mL</td>
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<td>50 mL</td>
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<td></td>
<td></td>
<td></td>
<td>100 mL</td>
<td>$1,055.12</td>
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<td></td>
<td></td>
<td>200 mL</td>
<td>$2,110.24</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mL</td>
<td>$4,220.49</td>
</tr>
<tr>
<td>Cuvitru</td>
<td>Baxalta US Inc.</td>
<td>PI (≥2 years of age)</td>
<td>SC</td>
<td>Solution</td>
<td>20%</td>
<td>5 mL</td>
<td>$168.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mL</td>
<td>$336.00</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>20 mL</td>
<td>$672.00</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 mL</td>
<td>$1,344.00</td>
</tr>
<tr>
<td>Hizentra</td>
<td>CSL Behring LLC</td>
<td>PI (≥2 years of age)</td>
<td>SC</td>
<td>Solution</td>
<td>20%</td>
<td>5 mL</td>
<td>$168.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mL</td>
<td>$336.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 mL</td>
<td>$672.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mL</td>
<td>$1,680.00</td>
</tr>
<tr>
<td>HyQvia</td>
<td>Baxalta Inc.</td>
<td>PI (adults)</td>
<td>SC</td>
<td>Solution</td>
<td>20%</td>
<td>26.25 mL</td>
<td>$462.50</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mL</td>
<td>$925.00</td>
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<td></td>
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<td></td>
<td>105 mL</td>
<td>$1,850.00</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>210 mL</td>
<td>$3,700.00</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>315 mL</td>
<td>$5,550.00</td>
</tr>
</tbody>
</table>

Abbreviations: B-CLL=B-cell Chronic Lymphocytic Leukemia, CIDP=Chronic Inflammatory Demyelinating Polyneuropathy, FDA=Food and Drug Administration, gm=gram, ITP=Immune Thrombocytopenic Purpura, IV=intravenous, mg=milligram, mL=milliliter, MMN=Multifocal Motor Neuropathy, PI=Primary Humoral Immunodeficiency, SC=subcutaneous

WAC as of 2/8/2017

Indications based on FDA-approved labeling as of 2/8/2017
tremely important that payors choosing to implement preferred product policies consider an exception process to ensure these members can maintain continued access to appropriate IG products when medically necessary. Table 2 provides a description of the IgA content and stabilizer used for each of the various products.

Another area of focus among payors’ management programs is the duration of approval for IG products. For patients with lifelong diseases such as PIDs, IG treatment will be lifelong and payors will typically authorize longer durations of approval (e.g. 12 months or longer).25 For off-label indications, however, payors have more flexibility in determining the duration of approval that will be authorized for IG product requests. One example of an off-label indication for which payors have implemented a limited duration of approval policy is autoimmune mucocutaneous blistering disease.26

Some payors have opted to limit the duration of approval to the short-term setting after the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination for the use of IVIG in treating specific subtypes of biopsy-proven autoimmune mucocutaneous blistering disease.26 In the determination memo, CMS indicated that contractors reserve the discretion to determine what constitutes short-term therapy.26 Other off-label indications may not have such detailed guidance, thus leaving payors with the task of determining durations of approval (e.g. 3 months vs 6 months vs longer duration of approval) for these indications based on supporting literature and clinical trials.

Payors have recently started employing SOC management programs for infused therapies; however, payors have primarily implemented these programs in other costly therapeutic areas, such as gastroenterology and rheumatology, leaving the management of SOC for patients receiving IG products relatively untouched. According to the National Infusion Center Association (NICA), the administration of infused therapies in a hospital outpatient setting is consistently more costly than other sites.27 Of note, administration at preferred SOCs such as home based infusion, provider offices, and/or specialty care clinics can eliminate unnecessary costs and therefore reduce waste. Generally, infusions administered at a preferred SOC can provide 20% to 60% savings when compared to a hospital outpatient setting.28 Based on the findings of an independent analysis of the top ten infused specialty medications, the average costs of these drugs in a hospital outpatient setting are 86% higher when compared to alternate sites.28 A separate analysis indicated that in 2013, the cost per claim for Gammagard Liquid29 was $6,590 in the hospital outpatient setting, $5,368 in a physician office, and $3,813 through home infusion/specialty pharmacy, highlighting the cost savings opportunity associated with alternate SOCs.29

In addition, managed care payors believe that alternate SOCs can offer high quality care in addition to lower treatment costs.30 Research has also indicated that lower coinurances, when applicable, and more convenient settings have been well received by members, leading to higher satisfaction.31 An IG-focused SOC program may also assist payors in reducing per-member-per-month (PMPM) costs, which have increased between 2010 and 2014 from $1.33 to $1.56 for commercial plans and $2.17 to $2.34 for Medicare plans, according to a medical pharmacy trends report.7

### TABLE 2. STABILIZER AND IGA CONTENT FOR IG PRODUCTS

<table>
<thead>
<tr>
<th>Product Names</th>
<th>Stabilizer</th>
<th>IgA Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Privigen</td>
<td>No sugar</td>
<td>&lt;25 mcg/mL</td>
</tr>
<tr>
<td>Octagam</td>
<td>Maltose</td>
<td>&lt;100 mcg/mL</td>
</tr>
<tr>
<td>HyQvia</td>
<td>No sugar</td>
<td>37 mcg/mL</td>
</tr>
<tr>
<td>Hizentra</td>
<td>No sugar</td>
<td>≤50 mcg/mL</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>No sugar</td>
<td>46 mcg/mL</td>
</tr>
<tr>
<td>Gammaphorix</td>
<td>Sorbitol</td>
<td>&lt;10 mcg/mL</td>
</tr>
<tr>
<td>Gammagard S/D</td>
<td>No sugar</td>
<td>&lt;2.2 mcg/mL</td>
</tr>
<tr>
<td>Gammagard Liquid</td>
<td>No sugar</td>
<td>&lt;37 mcg/mL</td>
</tr>
<tr>
<td>Flebogamma 10% DIF</td>
<td>Sorbitol</td>
<td>&lt;100 mcg/mL</td>
</tr>
<tr>
<td>Flebogamma 5% DIF</td>
<td>Sorbitol</td>
<td>&lt;50 mcg/mL</td>
</tr>
<tr>
<td>Cuvitru</td>
<td>No sugar</td>
<td>80 mcg/mL</td>
</tr>
<tr>
<td>Gammaplex</td>
<td>Sorbitol</td>
<td>&lt;10 mcg/mL</td>
</tr>
<tr>
<td>Carimune NF</td>
<td>Sucrose</td>
<td>&lt;720 mcg/mL</td>
</tr>
<tr>
<td>Bivigam</td>
<td>No sugar</td>
<td>≤200 mg/mL</td>
</tr>
</tbody>
</table>

Table adapted from respective package inserts

**Potential Solutions to Improve Management of Treatment-Related Costs**

The process of effectively implementing an IG SOC management program involves numerous steps, various considerations, and multiple parties. The first and most important step in SOC program development involves an in-depth analysis of medical and pharmacy data to identify which factors are driving the utilization of certain products at each SOC, as well as an assessment of what potential economic opportunities exist for each product within the class.29 This first step is crucial in determining what preferred product strategy a payor should use. Beyond the economic considerations, the preferred product determination process should also include a thorough...
“A recent medical pharmacy trend report indicated that the annual cost for IVIG per patient in the commercial setting was comparable, with annual costs primarily in the range of $40,000 to $50,000.”

PAYORS MAY WANT TO FOCUS ON PRODUCT CHARACTERISTICS, PARTICULARLY ROUTE OF ADMINISTRATION, STRENGTH, AND PACKAGE SIZE.

Payors may want to focus on products that can be administered IV or SC to allow for greater flexibility in SOC choice and also identify which products have the highest utilization among their plan members to analyze the level of disruption that could occur with any potential changes in preferred products. Regardless of the ultimate preferred product decision, it is highly recommended that payors communicate any such changes to both providers and patients with sufficient notice of change in order to minimize treatment disruption and ensure that members for whom there is medical necessity for a particular treatment are not subject to preferred product restrictions.

It is also important that payors determine what prescriber restrictions, if any, will be placed on IG product prior authorization requests. For example, payors may choose to limit coverage of IG products to prescribers who specialize in immunology, oncology, neurology, or any other FDA-approved areas of use or off-label use deemed medically necessary by the plan. As mentioned previously, duration of approval should be a large consideration, with an emphasis on providing longer durations of approval for members with chronic diseases that will require lifelong treatment and shorter durations of approval for members with conditions for which IG products have evidence for use only in the short-term setting.

Consideration should be given to the notion that not all patients will be candidates for IG administration at alternate SOCs. The American Academy of Allergy Asthma & Immunology (AAAAI) has published guidelines for SOC administration of IVIG therapy which note that every initial infusion of and change in product for IVIG should be administered under physician supervision in a facility that is equipped to handle the most severe of acute medical complications. The guidelines also indicate that certain patients may continue to require higher levels of monitoring and intervention during infusions and patients who have tolerated therapy without a history of adverse events may be considered for lower levels of supervision during infusions.

Of note, AAAAI has identified specific patient groups of focus when developing SOC management programs: 1) patients requiring chronic IVIG therapy and have had a severe IVIG adverse event and for whom the physician is uncomfortable utilizing hospital outpatient physician-/nurse-supervised infusions or physician office based physician-/nurse-supervised infusion; 2) patients requiring chronic IVIG therapy and have had an adverse reaction that is not easily managed by mild premedication; 3) patients receiving a particular product without adverse events or mild adverse events that can easily be managed with mild premedication; and 4) patients who do not experience IVIG infusion-related adverse events, have a high level of medical sophistication, and have a trained partner available to assist with adverse event management during infusions. The guidelines do note, however, that for patient group 1, administration could still occur in the hospital outpatient or physician office based physician-/nurse-supervised settings if more intensive monitoring occurs. AAAAI also recognizes that physician office based physician-/nurse-supervised infusions may not be feasible for all patients due to geographic challenges which highlights the importance of incorporating geographical considerations into the payor’s decision-making process. Additionally, in order for patients to be considered eligible for home-based infusion with nurse supervision, patients must be physically and cognitively able to comply with the treatment regimen and schedule. For patients to be considered eligible for home-based infusion with partner supervision, both the patient and the partner must undergo specific training and demonstrate competence in infusion administration.

Beyond proper administration technique and training on safety and the importance of adherence, patients should also be educated about the potential benefits of IG product administration in alternate SOCs. For example, there are varying degrees of immunosuppression among patients who have PID, some of whom are severely immunosuppressed. This patient population is at high risk of contracting infections or illnesses while in a hospital or office setting and thus, may benefit from home infusions where there is a decreased risk for exposure to infectious diseases. Additionally, for patients whose schedules are negatively impacted by frequent hospital or office visits and are physically and cognitively able to self-administer in their own homes, home-based administration may be an attractive option that allows them to continue treatment without disruptions to their work-life balance. In instances where there is an economic benefit to implement an SOC policy that focuses on specific SOCs, payors should consider sharing the savings with members by providing incentives to drive uptake. Additionally, given that these prior authorization requests may be denied for any number of reasons, a process for peer-to-peer reviews should be designed to allow for discussion surrounding why a patient may not be a candidate for IG product switches, alternate SOC administration,
shorter duration of treatment, or any other reason for medical necessity.

The trend of optimizing alternate SOCs for members receiving infused therapies has shown no signs of abating and it is expected that this trend will continue to grow, particularly in high cost therapeutic areas in which patients require lifelong treatment for chronic conditions. The process of optimizing SOCs is multifactorial and requires a thorough analysis of the medical and pharmacy data prior to program implementation and careful consideration of the potential impact of preferred product changes on plan members. Additionally, program implementation will require contract renegotiation among the various SOC entities as well as patient and provider education to minimize disruption.

In conclusion, SOC optimization for IG products may represent a prime area for substantial cost savings and it is recommended that payors reassess their current efforts in this category to determine what additional cost savings opportunities may exist for their organizations.

REFERENCES

Navigating the challenges of HIV requires innovation

ViiV Healthcare can help

As the only company solely focused on HIV, ViiV Healthcare can help you better understand and meet the needs of your members living with HIV.

ViiV Healthcare is a global specialist HIV company dedicated to delivering advances in treatment and care for people living with HIV. The company’s aim is to take a deeper and broader interest in HIV/AIDS than any company has done before, and take a novel approach to delivering new and effective HIV medicines, as well as supporting communities affected by HIV.

Connect with us at www.viivhealthcare.com
The Next Wave of Specialty Pharmacy: The Ever-Changing Diabetes Landscape

The rapid influx of specialty pharmaceuticals in the prescription drug landscape has not gone unnoticed by payors. According to the Academy of Managed Care Pharmacy (AMCP), specialty drugs are medications that typically require special handling, storage, administration, monitoring, and/or support.¹ The American Journal of Managed Care (AJMC) notes that another common definition of specialty pharmaceuticals focuses on drugs with prices above $600/month and treat rare conditions, require special handling, use a limited distribution network, or require ongoing clinical assessment.² It is important to note, however, that no universal definition or classification system exists, giving payors flexibility in determining which drugs will be designated as “specialty pharmaceuticals.” This same flexibility also presents a challenge for payors, as there is little guidance regarding appropriate therapeutic class evaluation and management strategies, especially for therapeutic classes, such as antihyperglycemics, that did not previously comprise specialty drugs. Once consisting of oral antidiabetics and traditional forms of injectable insulin, the antihyperglycemic therapeutic class has since expanded to include a number of other pharmacotherapies, including extended-release insulin, mixed insulins, and even injectable biologics. The ever-changing diabetes landscape, impacted by the emergence of more costly injectable therapies, may now be transitioning into a specialty disease state that is sure to draw further attention from payors.

Current Treatment Guidelines and Economic and Clinical Considerations

The complex nature of diabetes requires a coordinated, chronic care model that emphasizes proactive care delivery and use of evidence-based care guidelines. Approaches to glycemic treatment for type 1 and type 2 diabetes include recommendations from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE).

The ADA recommends the following pharmacological management strategies, with a treatment selection decision-making process focused on efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences:³

- Type 1: Multiple-dose insulin (MDI) injections or continuous subcutaneous insulin infusion (CSII); use of insulin analogs to reduce the risk of hypoglycemia; and consideration for the use of a sensor-augmented low glucose threshold suspend pump, particularly for patients at risk for hypoglycemia.
• Type 2: While lifestyle changes are considered first-line therapy, the progressive nature of diabetes results in many patients eventually requiring insulin therapy. Metformin, an oral medication, is the preferred first-line pharmacological therapy if lifestyle changes do not achieve or maintain glycemic goals. For newly diagnosed patients who are markedly symptomatic and/or have elevated blood glucose levels or A1C, insulin therapy, alone or in combination with additional agents, should be considered. If A1C targets are not achieved after three months of treatment with metformin monotherapy, dual therapy should be initiated. A dual therapy regimen consists of metformin in combination with an agent from one of the following therapeutic classes:

The AACE and ACE recommend the following pharmacological management strategies, with treatment selection based on factors including, but not limited to, treatment efficacy, cost, and risk of hypoglycemia, weight gain, and side effects, and patient-specific considerations, such as adherence and comorbidities:

- Type 2: Similar to the ADA guidelines, AACE/ACE guidelines recommend lifestyle changes as first-line therapy. Of note, AACE/ACE guidelines suggest that in patients with an entry A1C <7.5%, dual therapy consisting of metformin in combination with an at least one other agent. Of note, AACE/ACE guidelines suggest that in patients with an entry A1C ≥7.5%, dual therapy consisting of metformin in combination with an additional agent is considered first-line therapy, the potential for hypoglycemia, weight gain, and side effects, and patient-specific considerations, such as adherence and comorbidities:

**Sulfonylureas**

- Amaryl® (gliclazide)
- Glucotrol® (glipizide)
- Micronase®, Diabeta®, Glucotrol® (glipizide)
- Amaryl® (glimepiride)
- Glynase® (glyburide)

**Dipeptidyl peptidase-4 (DPP-4) inhibitors**

- Nesina® (alogliptin)
- Tradjenta® (linagliptin)
- Januvia® (sitagliptin)

**Sodium-glucose co-transporter 2 (SGLT2) inhibitors**

- Invokana® (canagliflozin)
- Farxiga® (dapagliflozin)
  - Jardiance®
  - Jardiance®

**Glucagon-like peptide 1 (GLP-1) receptor agonists**

- Byetta®, Bydureon®
- Byetta®, Bydureon®

**Basal insulin, long-acting**

- Tesibra® (degludec)
  - Jardiance®
  - Jardiance®

**Basal insulin, intermediate-acting NPH**

- Humulin® N, Novolin® N
- Humulin® N, Novolin® N

**Basal insulin, long-acting**

- Lantus® (glargine)
- Lantus® (glargine)

**Basal insulin, intermediate-acting NPH**

- Micronase®, Diabeta®, Glucotrol® (glipizide)
- Amaryl® (glimepiride)
- Tolinase® (tolazamide)

**DPP-4 inhibitors**

- Nesina® (alogliptin)
- Tradjenta® (linagliptin)
- Januvia® (sitagliptin)

**SGLT2 inhibitors**

- Invokana® (canagliflozin)
- Farxiga® (dapagliflozin)
- Jardiance®

**GLP-1 receptor agonists**

- Byetta®, Bydureon®
- Byetta®, Bydureon®

**Basal insulin**

- Humulin® N, Novolin® N
- Humulin® N, Novolin® N

**Sulfonylureas**

- Amaryl® (gliclazide)
- Glucotrol® (glipizide)
- Micronase®, Diabeta®, Glucotrol® (glipizide)
- Amaryl® (glimepiride)
- Glynase® (glyburide)

**Dipeptidyl peptidase-4 (DPP-4) inhibitors**

- Nesina® (alogliptin)
- Tradjenta® (linagliptin)
- Januvia® (sitagliptin)

**Sodium-glucose co-transporter 2 (SGLT2) inhibitors**

- Invokana® (canagliflozin)
- Farxiga® (dapagliflozin)
- Jardiance®

**Glucagon-like peptide 1 (GLP-1) receptor agonists**

- Tanzeum® (albiglutide)
- Trulicity® (licoglucerase)
- Byetta®, Bydureon® (exenatide, exenatide long-acting)

**Basal insulin, long-acting**

- Tesibra® (degludec)
  - Jardiance®
  - Jardiance®

**Basal insulin, intermediate-acting NPH**

- Humulin® N, Novolin® N
  - Humulin® N, Novolin® N

**Sulfonylureas**

- Amaryl® (gliclazide)
- Glucotrol® (glipizide)
- Micronase®, Diabeta®, Glucotrol® (glipizide)
- Amaryl® (glimepiride)
- Glynase® (glyburide)

**Dipeptidyl peptidase-4 (DPP-4) inhibitors**

- Nesina® (alogliptin)
- Tradjenta® (linagliptin)
- Januvia® (sitagliptin)

**Sodium-glucose co-transporter 2 (SGLT2) inhibitors**

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- Farxiga® (dapagliflozin)
- Jardiance®

**Glucagon-like peptide 1 (GLP-1) receptor agonists**

- Tanzeum® (albiglutide)
- Trulicity® (licoglucerase)
- Byetta®, Bydureon® (exenatide, exenatide long-acting)

**Basal insulin, long-acting**

- Tesibra® (degludec)
  - Jardiance® (empagliflozin)

**Basal insulin, intermediate-acting NPH**

- Humulin® N, Novolin® N
  - Humulin® N, Novolin® N
# AVAILABLE DIABETES TREATMENTS: PRICING AND A1C REDUCTION

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Wholesale Acquisition Cost (WAC)/package</th>
<th>A1C, Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALPHA-GLUCOSIDASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precose®, others (acarbose)</td>
<td>100 mg/100 tablets - $62.30</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>Glyset® (miglitol)</td>
<td>100 mg/100 tablets - $223.27</td>
<td>0.5 – 1.0</td>
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<tr>
<td><strong>BIGUANIDE MONOTHERAPY, COMBINATION THERAPY</strong></td>
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<tr>
<td>Fortamet®, Glucophage®, Glucophage XR®, Glumetza®, Riomet® (metformin)</td>
<td>500 mg/100 tablets - $6.26</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Kazano® (alogliptin/metformin)</td>
<td>12.5 mg/1,000 mg/60 tablets - $374.33</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>Jentadueto®, Jentadueto® XR (linagliptin/metformin, linagliptin/metformin extended-release)</td>
<td>2.5 mg/1,000 mg/60 tablets - $381.00</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>Kombiglyze® XR (saxagliptin/metformin)</td>
<td>5 mg/1,000 mg/30 tablets - $385.14</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>Janumet®, Janumet® XR (sitagliptin/metformin, sitagliptin/metformin extended-release)</td>
<td>50 mg/1,000 mg/60 tablets - $381.00</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Xigduo® XR (dapagliflozin/metformin extended-release)</td>
<td>10 mg/1,000 mg/30 tablets - $430.52</td>
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<tr>
<td>Synjardy® (empagliflozin/metformin)</td>
<td>12.5 mg/1,000 mg/60 tablets - $430.51</td>
<td>0.7 – 0.8</td>
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<tr>
<td>Actoplus MET® (pioglitazone/metformin)</td>
<td>15 mg/850 mg/60 tablets - $75.00</td>
<td>0.8 – 1.0</td>
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<tr>
<td>Actoplus MET® XR (pioglitazone/metformin)</td>
<td>30 mg/1,000 mg/30 tablets - $633.60</td>
<td>0.8 – 1.0</td>
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<tr>
<td>Avandamet® (rosiglitazone/metformin)</td>
<td>2 mg/1,000 mg/60 tablets - $137.76</td>
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<tr>
<td><strong>BILE ACID SEQUESTRANT</strong></td>
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<tr>
<td>Welchol® (colesevelam)</td>
<td>625 mg/180 tablets – $565.20</td>
<td>0.5 – 1.0</td>
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<tr>
<td><strong>DOPAMINE AGONIST</strong></td>
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<tr>
<td>Parlodex®, Cycloset® (bromocriptine)</td>
<td>5 mg/30 capsules - $268.51</td>
<td>0.5 – 1.0</td>
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<tr>
<td><strong>DPP-4 INHIBITORS</strong></td>
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<tr>
<td>Nesina® (alogliptin)</td>
<td>25 mg/30 tablets - $374.33</td>
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<tr>
<td>Tradjenta® (linagliptin)</td>
<td>5 mg/30 tablets - $381.00</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>Onglyza® (saxagliptin)</td>
<td>5 mg/30 tablets - $385.14</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Januvia® (sitagliptin)</td>
<td>100 mg/30 tablets - $381.00</td>
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<tr>
<td><strong>MEGLITINIDES</strong></td>
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<tr>
<td>Starlix® (nateglinide)</td>
<td>120 mg/100 tablets - $343.04</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Prandin® (repaglinide)</td>
<td>2 mg/100 tablets - $625.61</td>
<td>0.5 – 1.0</td>
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<tr>
<td><strong>SGLT2 INHIBITORS</strong></td>
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<tr>
<td>Invokana® (canagliflozin)</td>
<td>100 mg/30 tablets - $391.74</td>
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<tr>
<td>Farxiga® (dapagliflozin)</td>
<td>10 mg/30 tablets - $430.52</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Jardiance® (empagliflozin)</td>
<td>25 mg/30 tablets - $430.51</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Glyxambi® (empagliflozin/linagliptin)</td>
<td>25 mg/5 mg/30 tablets - $523.57</td>
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<tr>
<td><strong>SULFONYLUREAS</strong></td>
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<tr>
<td>Amaryl® (glimepiride)</td>
<td>4 mg/100 tablets - $8.94</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Glucotrol® (glipizide)</td>
<td>10 mg/100 tablets - $6.10</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Glipizide XL® (glipizide extended release)</td>
<td>10 mg/100 tablets - $31.70</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Micronase®, Diabeta®, Glynase® (glyburide)</td>
<td>5 mg/100 tablets - $24.65</td>
<td>1.0 – 1.5</td>
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</tbody>
</table>
### AVAILABLE DIABETES TREATMENTS: PRICING AND A1C REDUCTION

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Wholesale Acquisition Cost (WAC)/package*</th>
<th>A1C, Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TZD</strong></td>
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<tr>
<td>Actos® (pioglitazone)</td>
<td>45 mg/30 tablets - $13.98</td>
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<tr>
<td>Osen® (pioglitazone/alogliptin)</td>
<td>25 mg/45 mg/30 tablets - $37.43</td>
<td>1.2 – 1.7</td>
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<tr>
<td>Avandia® (rosiglitazone)</td>
<td>4 mg/30 tablets - $161.37</td>
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<tr>
<td><strong>NON-INSULIN INJECTABLES</strong></td>
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<td><strong>AMYLIN ANALOG</strong></td>
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<tr>
<td>SymlinPen® (pramlintide)</td>
<td>1,000 mcg/1 mL (2.7 mL autoinjector) - $973.53</td>
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<tr>
<td><strong>GLP-1 RECEPTOR AGONISTS</strong></td>
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<tr>
<td>Tanzeum® (albiglutide)</td>
<td>50 mg (4 syringes) - $478.91</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Trulicity® (dulaglutide)</td>
<td>1.5 mg/0.5 mL (4 syringes) - $626.00</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Byetta® (exenatide)</td>
<td>250 mcg/1 mL (2.4 mL prefilled pen) - $668.28</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Bydureon® (exenatide, long-acting)</td>
<td>2 mg (4 prefilled pens) - $622.79</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Victoza® (liraglutide)</td>
<td>6 mg/1 mL (3 pens) - $747.63</td>
<td>1.0 – 1.5</td>
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<tr>
<td>Adlyxin® (lixisenatide)</td>
<td>100 mcg/1 mL (2 prefilled pens) - $557.20</td>
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<tr>
<td><strong>COMBINATION GLP-1 RECEPTOR AGONIST/INSULIN</strong></td>
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<tr>
<td>Xultophy® (insulin degludec/liraglutide)</td>
<td>100 units/3.6 mg/1 mL (5 prefilled pens) - $953.18</td>
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<tr>
<td>Soliqua® (insulin glargine/lixisenatide)</td>
<td>100 units/33 mcg/1 mL (5 prefilled pens) - $635.00</td>
<td>1.5 – 2.0</td>
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<tr>
<td><strong>BASAL INSULIN</strong></td>
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<tr>
<td>Humulin® N, Novolin® N (insulin isophane)</td>
<td>100 units/1 mL (10 mL vial) - $137.90</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td><strong>INTERMEDIATE-ACTING</strong></td>
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<tr>
<td>Tresiba® (insulin degludec)</td>
<td>100 units/1 mL (3 mL) - $443.85</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td>Ryzodeg® (insulin degludec/insulin aspart)</td>
<td>Pricing unavailable</td>
<td>1.5 – 3.5</td>
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<tr>
<td>Levemir® (insulin detemir)</td>
<td>100 units/1 mL (10 mL vial) - $269.00</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td>Lantus® (Insulin glargine)</td>
<td>100 units/1 mL (10mL) - $248.51</td>
<td>1.5 – 3.5</td>
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<tr>
<td>Toujeo® (insulin glargine)</td>
<td>300 units/1 mL (1.5 mL prefilled pen) - $335.48</td>
<td>1.5 – 3.5</td>
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<tr>
<td><strong>LONG-ACTING</strong></td>
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<tr>
<td>Apidra® (insulin glulisine)</td>
<td>100 units/1 mL (10 mL vial) - $255.11</td>
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<tr>
<td>Humalog® (insulin lispro)</td>
<td>100 units/1 mL (10 mL vial) - $254.80</td>
<td>1.5 – 3.5</td>
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<tr>
<td>Humulin® R (insulin regular)</td>
<td>100 units/1 mL (10 mL vial) - $137.90</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td>Novolog® (insulin aspart)</td>
<td>100 units/1 mL (10 mL vial) - $255.40</td>
<td>1.5 – 3.5</td>
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<tr>
<td><strong>RAPID/SHORT-ACTING</strong></td>
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<tr>
<td>Humalog® Mix 75/25 (insulin lispro protamine, insulin lispro)</td>
<td>75 units/25 units/1 mL (10 mL vial) - $264.10</td>
<td>1.5 – 3.5</td>
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<tr>
<td>Humalog® Mix 50/50 (insulin lispro protamine, insulin lispro)</td>
<td>50 units/50 units/1 mL (10 mL vial) - $264.10</td>
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<tr>
<td>Humulin® 70/30 (insulin isophane, insulin regular)</td>
<td>70 units/30 units/1 mL (10 mL) - $137.90</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td>Novolin® 70/30 (insulin isophane, insulin regular)</td>
<td>70 units/30 units/1 mL (10 mL) - $137.70</td>
<td>1.5 – 3.5</td>
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<tr>
<td>Novolog® 70/30 (insulin aspart protamine, insulin aspart)</td>
<td>70 units/30 units/1 mL (10 mL) - $264.90</td>
<td>1.5 – 3.5</td>
</tr>
</tbody>
</table>


*Micromedex. Red Book Online. WAC as of 2/7/2017

When WAC is unavailable, AWP is substituted. When generic is available, the reported WAC refers to the generic product.
approval for biosimilars, which will likely limit the associated cost savings when compared with the cost savings typically associated with the availability of generic drugs. Still, the cost of biosimilar insulins may represent a 15% to 30% discount compared to their reference products.14,15

While interest in biosimilar insulin is high, there are no biosimilar insulin products available in the United States. In Europe, Abasaglar® (reference product: Lantus® [Sanofi Aventis]), manufactured by Lilly and Boehringer Ingelheim, is the only biosimilar insulin product on the market.16 In the United States, Basaglar® (insulin glargine, Lilly) was approved by the FDA in December 2015 as a follow-on biologic, rather than a biosimilar.17 Basaglar® (insulin glargine), which launched in 2016, is the first insulin product approved through an abbreviated pathway that relied on the known safety and efficacy of Lantus®, similarities between the follow-on biologic and the reference product, and two clinical trials of patients with type 1 and type 2 diabetes.17 Of note, there is an insulin lispro follow-on biologic (reference product: Humalog [insulin lispro], Lilly) for both type 1 and type 2 diabetes mellitus (SAR342434, Sanofi) under regulatory review by the European Union.18

Beyond biosimilar development, one new chemical entity, two new combination therapies, and two new formulations of existing products received FDA approval in 2016. The newly-approved, once-daily, GLP-1 receptor agonist, Adylyxin® (lixisenatide, Sanofi Aventis), received FDA approval in July 2016.9 In addition, two combination products, Xultophy® (insulin degludec/liraglutide, Novo Nordisk) and Soliqua™ (insulin glargine/lixisenatide, Sanofi Aventis), both received FDA approval in late November 2016.8,19 Two new formulations of existing products, Jentadueto® XR (lixiaglaptin/metformin extended-release, Lilly) and Invokamet® XR (canagliflozin/metformin extended-release, Janssen), also received FDA approval in May and September of 2016, respectively.20,21 There are numerous other new chemical entities in phase III development and under regulatory review which will be discussed later in this article.

Implications for Managed Care

In 2013, the average annual medical expenditure for patients with diabetes was $13,700, with nearly $8,000 of those costs attributed to the disease itself.22 Escalating prescription drug costs, particularly for insulin in recent years, and the emergence of various new products and formulations have positioned diabetes as an important focus area for managed care decision makers.

While oncology therapies and biologic drugs for autoimmune disorders represent the biggest drivers of specialty spending, the rising costs and rapidly changing product landscape may result in payors beginning to implement strategies that mirror specialty drug benefit management approaches to control the prescription drug costs associated with the management of diabetes.23 The new chemical entities and branded combinations of existing products may offer clinical advantages, such as reduced likelihood of hypoglycemia and improved ease of self-administration, respectively; however, coordinat ed disease management is necessary to manage outcomes and comorbidities. Payor strategies that may be beneficial in controlling diabetes-related pharmacy costs, managing access to new therapies, and improving outcomes include the following:

1. Prior authorizations (PAs)
2. Step therapy requirements
3. Designation of preferred products
4. Use of multiple tiers
5. Use of limited distribution networks, including specialty pharmacies
6. Implementation of clinical programs, including adherence monitoring

Due to the high costs associated with the newer therapies and the increasing costs of older products, payors may consider implementing a PA program or adjusting their existing PA program to reflect the new additions to the diabetes treatment landscape. Each organization’s decision makers should ensure that patients have access to evidence-based treatments and PA decisions should be based on cost of treatment, previously therapies, level of control with current regimen, and potential improvements in A1C with the requested treatment, as well as other plan-specific determination factors.

The aforementioned evidence-based guidelines each suggest a hierarchy of product selection, most often beginning with metformin, due to its efficacy, tolerability, and affordability. Payors choosing to implement step therapy requirements should consider utilizing these guidelines to determine which products will be considered first-, second-, and third-line agents, and even which agents will be considered in the treatment-refractory setting.

Given the large number of prescription drugs within each class of antihyperglycemics, payors may want to consider selecting one or more preferred products within each specific class of drugs. Many agents within a class of drugs share similar A1C reduction profiles, but may differ in cost, tolerability, and financial agreements. Payors should be mindful of these opportunities to work with manufacturers to improve cost savings while minimizing the potential to compromise patient care.

With the advent of specialty drugs, many payors have expanded their tiering structure to include a specialty tier. Within the antihyperglycemic therapeutic class, there is a wide range of product availability, including generic oral drugs, branded oral and injectable therapies, and biologics. Based on the tiering structure, payors may consider positioning certain high cost injectable insulins and/or biologics within their specialty tier, if applicable.

Due to the unique storage, handling, and administration requirements of some of these new-to-market drugs, specialty pharmacies may represent a more appropriate avenue for prescription dispensing.

The majority of innovation within the diabetes landscape has been fueled by the increased number of injectable therapies. Payors should pay careful attention to patients’ medication adherence with these injectable therapies, as there is a high cost associated with the potential waste of these drugs. To reduce waste, payors should consider implementing clinical programs that focus on addressing barriers to, and improving levels of, adherence.
“A recent analysis demonstrated that insulin costs have more than tripled over the last decade.”

strategies, payors may consider the use of additional restrictions to manage drug spend within the antihyperglycemic class. Specifically, payors may consider transitioning prescription coverage to the specialty pharmacy benefit. As there is no universal definition of “specialty drug,” payors may determine that some of the higher cost injectables belong in the specialty drug category and possibly consider restricting coverage to the specialty pharmacy benefit. If payors designate certain products within this therapeutic class as specialty drugs, consideration should be given to restricting dispensing to limited distribution networks, such as specialty pharmacies, which may be better equipped to dispense these medications and potentially execute clinical programs with an emphasis on medication adherence.

Diabetes Pharmaceutical Pipeline – What’s on the Horizon?

The pace of diabetes treatment research shows no signs of slowing down. Of note, a number of diabetes treatments in the pharmaceutical pipeline have caught the attention of payors: one single-agent GLP-1 receptor agonist (semaglutide, Novo Nordisk) in both oral and injectable formulations, one faster-acting insulin aspart (NN1218, Novo Nordisk), and one new chemical entity SGLT 2 inhibitor (ertugliflozin, Pfizer) as both a single agent and two additional combination formulations (ertugliflozin/sitagliptin, Pfizer and Merck, and ertugliflozin/metformin, Pfizer and Merck).24-26

In a recent phase III trial, treatment with the once-weekly GLP-1 receptor agonist, semaglutide (Novo Nordisk), resulted in reductions in A1C levels.27 A specific timeline for projected market entry is not available for injectable semaglutide at this time; however, the manufacturer announced the submission of a new drug application (NDA) to the FDA in December 2016.28 Additionally, a once-daily oral formulation of semaglutide (Novo Nordisk) is in phase III development, with an unknown timeline for projected market entry as well.23 An NDA was submitted to the FDA for the faster-acting insulin aspart (NN1218, Novo Nordisk) in December 2015.29 The manufacturer received a complete response letter from the FDA in October 2016 and announced that it is currently reviewing the letter and plans to work closely with the FDA to resolve any outstanding issues.30 Lastly, treatment with ertugliflozin monotherapy (Pfizer and Merck), ertugliflozin/sitagliptin (Pfizer and Merck), and ertugliflozin/metformin (Pfizer and Merck) are all currently in phase III development and there is no information regarding regulatory submission for these products at this time.31

As the diabetes landscape continues to expand and costs rise, it becomes increasingly important for managed care decision makers to determine how their organizations will manage the antihyperglycemic drug class. With injectable therapies rising above the $600/month threshold and requiring special handling, administration, and monitoring, plans may determine that these recently-approved treatments and investigational agents in the pipeline may be classified as “specialty drugs,” thus requiring very different management strategies from the previously traditional antihyperglycemic class. Plans should consider the recommendations set forth in evidence-based guidelines, taking into account the cost of treatment, patient-specific factors, and clinical efficacy and safety, while also recognizing that their management strategies will be impacted by pending FDA approvals, follow-on biologics, and potentially biosimilars in the near future.

“With injectable therapies rising above the $600/month threshold and requiring special handling, administration, and monitoring, plans may determine that these recently-approved treatments and investigational agents in the pipeline may be classified as “specialty drugs.”
REFERENCES

THERE’S EYLEA—a treatment option that can fit your plans for proven visual acuity outcomes

✓ EYLEA has proven outcomes as demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME
✓ With monthly and every-other-month dosing, EYLEA offers flexible dosing options to meet the needs of your providers and your members

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS
- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

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

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

ADVERSE REACTIONS
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (>25%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

*The FDA-approved indications for EYLEA are Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME.
†After an initial monthly dosing period for certain indications.


Please see brief summary of full Prescribing Information on the following page.
3. Thromboembolic Events. There is a potential risk of arterial (thromboembolic events) following intravitreal use of VEGF inhibitors, including EYLEA. AEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of undetermined cause). The incidence of reported thromboembolic events in 2 AMD studies conducted the first year was 1.6% (32 out of 1843) in the combined group of patients treated with EYLEA. The incidence in the DME studies conducted from baseline to week 24 was 1.3% (19 out of 1470) in the combined group of patients treated with EYLEA compared with 2.2% (8 out of 297) in the control group; from baseline to week 100, the incidence was 6.4% (77 out of 1209) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the Warnings and Precautions section of this label:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thrombomembolism

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice. A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among these, 210 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in >10% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, castaneous, vitreous floaters, intraocular pressure increased, and ocular hypotension.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunassays. The incidence of antibodies to EYLEA is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to EYLEA may be different in different populations and settings.

Table 1: Most Common Adverse Reactions (≥5%) in Wet AMD Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=212)</th>
<th>VEGF Trap-Eye (N=287)</th>
<th>Active Control (N=595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>2%</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>5%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Castaneous</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Ocular hypotension</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Retinal pigment epithelium detachment</td>
<td>&lt;1%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Intravitreal injection site reaction</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal pigment epithelium hypotrophy</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Cataract</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
| Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hyperosmolarity, retinal detachment, rhegmatogenous, and endophthalmitis.

Table 2: Most Common Adverse Reactions (≥5%) in RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CRVO (N=328)</th>
<th>BRVO (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Intravitreal pressure increased</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Intraocular pressure decreased</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Ocular hypotension</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Foreign body sensation in eye</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Intravitreal injection site reaction</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
| Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were cataract, endophthalmitis, and vision loss.

Table 3: Most Common Adverse Reactions (≥5%) in DME Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td>Retinal pigment epithelium detachment</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Cataract</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Intravitreal pressure increased</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Foreign body sensation in eye</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Intraocular pressure decreased</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Ocular hypotension</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>
| Less common adverse reactions reported in <1% of the patients treated with EYLEA were hyperosmolarity, retinal detachment, rhegmatogenous, and injection site hemorrhage.

Less common adverse reactions reported in <1% of the patients treated with EYLEA were erythema, conjunctival edema, tinnitus, and conjunctival edema.

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (see (Worse vision)). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intravitreal pressure and the performed intravitreal injection must be monitored and managed appropriately (see Dosage and Administration).
Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 90% of all kidney cancers.¹ Due to various advances in both treatment and detection, the five-year survival rate for patients with kidney cancer has risen drastically from 34% in 1954 to 73% in 2011.²³ Unfortunately, however, the incidence of RCC is now threefold higher than the mortality rate, and the American Cancer Society has estimated that there would be nearly 63,000 new cases of RCC and approximately 14,000 deaths in the United States in 2016.⁴⁵ The European Society for Medical Oncology (ESMO) has published clinical practice guidelines for the diagnosis, treatment, and follow-up of RCC.⁶ For patients with metastatic RCC (mRCC), treatment recommendations are primarily for clear cell histology and depend on risk stratification.⁶ First-line treatment options for patients with good or intermediate prognosis include axitinib, sorafenib, or pazopanib and an alternative treatment option is sunitinib.⁶ For patients with poor risk, second-line treatment following tyrosine kinase inhibitor (TKI) therapy includes nivolumab or cabozantinib, with alternative treatment options including axitinib, everolimus, or sorafenib.⁶ Third-line treatment options for patients with good or intermediate risk depend on previous therapies.⁶ Following treatment with two TKIs, options include nivolumab and cabozantanib, with everolimus as an alternative.⁶ Following treatment with one TKI and a mechanistic target of rapamycin (mTOR), options include sorafenib, nivolumab, or cabozantinib, with another TKI or a re-challenge as potential alternatives.⁶ Third-line treatment options for patients with poor risk also depend on previous therapies.⁶ Following treatment with a TKI/nivolumab, the recommended treatment is cabozantanib, and alternative treatments include axitinib or everolimus.⁶ Following treatment with a TKI/cabozantinib, the recommended treatment is nivolumab, and alternative treatment options include everolimus and axitinib.⁶ The majority of first-line and subsequent therapies for both histological subtypes are molecular-targeted agents which have demonstrated prolonged PFS, overall survival (OS), or both.⁷

Of note, cabozantinib (Cabometyx™, Exelixis, Inc.) received Food and Drug Administration (FDA) approval in April 2016 for the treatment of advanced RCC in patients who have received prior anti-angiogenic therapy.⁸ The approval of cabozantinib was based on the results of an open-label study (N=658) in which patients with advanced RCC who had received prior anti-angiogenic therapy were randomized to receive oral cabozantinib 60 mg once daily or oral everolimus 10 mg once daily until disease progression or unacceptable toxicity.⁹ The study met its primary endpoint by demonstrating longer median PFS in patients who received cabozantinib compared to everolimus (7.4 vs 3.8 months, respectively; HR 0.58, 95% CI 0.45 to 0.74, P<0.0001).⁹ Median OS was also extended in the intent-to-treat population in the cabozantinib group compared to the everolimus group (21.4 vs 16.5 months, respectively; HR 0.66, 95% CI 0.53 to 0.83, P=0.0003).

Although cabozantinib has not received FDA approval for use in previously untreated patients, treatment with cabozantinib was recently studied in the CABOSUN trial (N=157) which enrolled adults with untreated, advanced or mRCC with a clear-cell component and measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and who were intermediate- or poor-risk according to the International
Patients were randomized to receive cabozantinib 60 mg once daily or sunitinib 50 mg once daily, utilizing a 4 weeks on/2 weeks off dosing schedule in the sunitinib treatment arm. The results of the study demonstrated that treatment with cabozantinib increased median PFS and was associated with a 34% reduction in the rate of progression or death compared to treatment with sunitinib (8.2 vs 5.6 months, respectively; adjusted HR 0.66, 95% CI, 0.46 to 0.95, one-sided P=0.012). At the cutoff time for publication of results, the study had not met its secondary endpoint of extended median OS in patients treated with cabozantinib compared to sunitinib (30.3 months vs 21.8 months, respectively; adjusted HR 0.80, 95% CI 0.50 to 1.26, NS), although there was a trend toward significance. It is important to note, however, that the results of the CABOSUN trial should not be compared directly to the results of other studies that evaluated sunitinib in the first-line setting for patients with advanced RCC.

The CABOSUN trial also evaluated the safety of treatment with either cabozantinib (N=78) or sunitinib (N=72). The results of the safety aspect of the trial demonstrated similar rates of treatment discontinuation due to adverse events (20% vs 21%, respectively), incidence of adverse events of any grade regardless of causality (99% in both groups), incidence of grade 3 or 4 adverse events (67% vs 68%, respectively), and incidence of grade 5 adverse events (5% vs 7%, respectively) between the cabozantinib and sunitinib treatment groups. Dose reductions occurred more commonly in patients treated with cabozantinib compared to sunitinib (58% vs 49%, respectively).

Based on the results of the trial, the manufacturer has announced its plans to submit a supplemental New Drug Application (sNDA) to the FDA for the use of cabozantinib as a first-line treatment option for advanced RCC. In the interim, the manufacturer has recommended that cabozantinib only be used in accordance with the approved product labeling, and thus should only be used in the previously treated patient population. Pending approval of the sNDA, treatment guidelines for kidney cancer will require updates to reflect any potential changes in product labeling for cabozantinib.

Presently, there are no recommendations regarding the specific order in which patients should receive molecular-targeted agents and major treatment guidelines include two category 1, preferred and two category 1 treatment recommendations for both first-line therapy and subsequent therapy options. If approved, cabozantinib may represent a third category 1, preferred or category 1, first-line therapy option for previously untreated patients who have advanced RCC. It is recommended that payors remain up to date regarding any potential approvals for supplemental indications or new treatments in this space in order to ensure patient access to appropriate and effective treatment options.
INDICATION

CABOMETYX™ (cabozantinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy.

WARNINGS AND PRECAUTIONS

IMPORTANT SAFETY INFORMATION

**CABOMETYX™** is the only single agent to demonstrate significant survival benefit in a phase III trial of patients with advanced RCC after prior treatment.*

**INDICATION**

CABOMETYX™ (cabozantinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy.

**WARNINGS AND PRECAUTIONS**

**Severe Hemorrhage** occurred with CABOMETYX™. Fatal hemorrhages also occurred in the cabozantinib clinical program. Do not administer CABOMETYX to patients who are at risk for or who have a recent history of severe hemorrhage.

**Gastrointestinal (GI) Perforations and Fistulas**, including anal fistula, were reported with CABOMETYX. Fatal perforations occurred in the cabozantinib clinical program. Monitor patients for symptoms. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

**Thrombotic Events**, including pulmonary embolism and arterial thromboembolism, increased with CABOMETYX. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction, cerebral infarction, or other serious arterial thromboembolic event.

**Hypertension and Hypertensive Crisis** increased with CABOMETYX. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy or medical management.

**Diarrhea** may be severe. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

**ADVERSE REACTIONS**

**Palmar-Plantar Erythrodysesthesia Syndrome (PPES)**, including anal fissure, were reported with CABOMETYX. Fatal perforations occurred in the cabozantinib clinical program. Evaluate for RPLS in patients who develop RPLS.

**Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment. CABOMETYX is not indicated for use in females who are or may become pregnant. If a pregnancy occurs in a woman receiving CABOMETYX, advise the patient to discontinue CABOMETYX and to use effective contraception during CABOMETYX treatment.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**, including cerebellar syndrome (CABS), were reported with CABOMETYX. Discontinue CABOMETYX in patients who experience a CABS or RPLS. CABOMETYX may be reinitiated at reduced doses if CABS or RPLS are adequately controlled with medical management.

**Hepatic Impairment**

In patients with mild to moderate hepatic impairment, reduce the dosage of CABOMETYX. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

**Neurotoxicity**

Severe neurotoxicity occurred with CABOMETYX. Discontinue CABOMETYX in patients who experience severe neurotoxicity. CABOMETYX may be reinitiated at reduced doses if neurotoxicity is adequately controlled with medical management.

**Concomitant Use with Strong CYP3A4 Inhibitors**

Concomitant use with strong CYP3A4 inhibitors cannot be avoided. CABOMETYX is not recommended for use in patients who are concomitantly treated with strong CYP3A4 inhibitors.

**Concomitant Use with Strong CYP3A4 Inducers**

Concomitant use with strong CYP3A4 inducers cannot be avoided. CABOMETYX is not recommended for use in patients who are concomitantly treated with strong CYP3A4 inducers.

**CABOMETYX™** is contraindicated in patients with diarrhea grades 3-4, hypertension grades 3-4, neutropenia, or severe anemia.

**RECOMMENDATION**

CABOMETYX is not recommended for use in patients with bilateral renal artery stenosis.

**EXCLUSION CRITERIA**

CABOMETYX is not recommended for use in patients with a prior history of severe hemorrhage.

**DO NOT USE**

Do not administer CABOMETYX to patients who are at risk for or who have a recent history of severe hemorrhage.
After prior therapy for advanced renal cell carcinoma (RCC),

**CHARGE FORWARD WITH THE POWER OF 3**

### PRIMARY ENDPOINT

<table>
<thead>
<tr>
<th>Median Overall Survival (OS)²:</th>
<th>Median Progression-free Survival (PFS)³:</th>
<th>Objective Response Rate (ORR)⁴:</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.4 months (CABOMETYX°)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs 16.5 months (everolimus)</td>
<td>7.4 months (CABOMETYX°)</td>
<td></td>
</tr>
<tr>
<td>(HR=0.66 [95% CI: 0.53-0.83]; P=0.0003)</td>
<td>(HR=0.58 [95% CI: 0.45-0.74]; P=0.0001)</td>
<td>17% vs 3% (CABOMETYX°)</td>
</tr>
<tr>
<td>(everolimus)</td>
<td>(everolimus)</td>
<td>(P=0.000)</td>
</tr>
</tbody>
</table>

*Confirmed per independent radiology review committee (IRRC).

**CABOMETYX™** is the only single agent to demonstrate significant improvement across 3 endpoints—OS, PFS, and ORR—in advanced RCC after prior treatment.*

*Anti-angiogenic therapy.

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**SECONDARY ENDPOINT**

- **Palmar-Plantar Erythrodysesthesia Syndrome (PPES)** occurred with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** occurred in the cabozantinib clinical program. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.

**ADVERSE REACTIONS**

The most commonly reported (>25%) adverse reactions were diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

**DRUG INTERACTIONS**

- **Avoid Strong CYP3A4 Inducers.** Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

**USE IN SPECIFIC POPULATIONS**

- **Avoid Strong CYP3A4 Inducers.** Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

**Please see Brief Summary of the Prescribing Information for CABOMETYX™ on adjacent pages.**


### CABOMETYX™

(cabozantinib) tablets

60 mg | 40 mg | 20 mg
CABOMETYX™ (COBZANTINIB) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic Therapy.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
Do not substitute CABOMETYX tablets with cabozantinib capsules.

The recommended daily dose of CABOMETYX is 60 mg. Do not administer CABOMETYX with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Continue treatment until patient no longer experiences clinical benefit or experiences unacceptable toxicity.

Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets. Do not take a missed dose within 12 hours of the next dose.

Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during CABOMETYX treatment.

2.2 Dosage Adjustments
For Patients Undergoing Surgery
Stop treatment with CABOMETYX at least 28 days prior to scheduled surgery, including dental surgery.

For Adverse Reactions
Without CABOMETYX for NCI CTCAE Grade 4 adverse reactions, and for Grade 3 or intolerable Grade 2 adverse reactions that cannot be managed with a dose reduction or supportive care.

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

• If previously receiving 60 mg daily dose, resume treatment at 40 mg daily
• If previously receiving 40 mg daily dose, resume treatment at 20 mg daily

• If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue CABOMETYX.

Permanently discontinue CABOMETYX for any of the following:

• development of unmanageable fistula or GI perforation
• severe hemorrhage
• arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
• hypertensive crisis or severe hypertensive medical condition
• nephrotic syndrome
• reversible posterior leukoencephalopathy syndrome

In Patients Concurrently Taking a Strong CYP3A4 Inhibitor
Reduce the daily CABOMETYX dose by 20 mg for example, from 60 mg to 40 mg daily or from 40 mg to 20 mg daily. Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

In Patients Concurrently Taking a Strong CYP3A4 Inducer
Increase the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of CABOMETYX should not exceed 80 mg.

In Patients with Hepatic Impairment
Reduce the starting dose of CABOMETYX to 40 mg once daily in patients with mild or moderate hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥ 3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program.

Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

5.2 GI Perforations and Fistulas
In a randomized study in renal cell carcinoma, fistulas were reported in 1.2% (including 0.6% anal fistulas) of CABOMETYX-treated patients and 0% of everolimus-treated patients. Gastrointestinal (GI) perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program.

Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

5.3 Thrombotic Events
CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.3% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX treatment resulted in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade ≥ 3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥ 3) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Without CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

5.5 Diarrhea
Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard anti-diarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to diarrhea occurred in 26% of patients.

5.6 Palmar-Plantar Erythrodysesthesia Syndrome (PPES)
Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

5.7 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.8 Embryo-fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to pregnant women. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
6.1 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.

The safety of CABOMETYX was evaluated in Study 1, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received 60 mg CABOMETYX and 322 patients received 10 mg everolimus administered daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 5% of CABOMETYX-treated patients included, in order of decreasing frequency: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, hypothyroidism, hypophosphatemia, hyponatremia, lymphocytopenia, decreased anemia, hyperkalemia, and GGT increased.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received ≥ 2 month reduction in CABOMETYX dose as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were; diarrhea, PPES, fatigue, and hypertension. Adverse reactions led to study treatment being held in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades 1</td>
<td>Grade 3 – 4</td>
</tr>
<tr>
<td></td>
<td>All Grades 1</td>
<td>Grade 3 – 4</td>
</tr>
<tr>
<td></td>
<td>Percentage (%) of Patients</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>28</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>Ulcerations</td>
<td>39</td>
<td>16</td>
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<tr>
<td>Weight decreased</td>
<td>31</td>
<td>12</td>
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<tr>
<td>Nervous System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>24</td>
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</tr>
<tr>
<td>Headache</td>
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<td>12</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>7</td>
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<tr>
<td>Endocrine Disorders</td>
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<tr>
<td>Hypothyroidism</td>
<td>21</td>
<td>&lt;1</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
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<tr>
<td>Dysphonia</td>
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<td>Dyspnea</td>
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<td>29</td>
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<tr>
<td>Quins</td>
<td>18</td>
<td>33</td>
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<tr>
<td>Blood and Lymphatic Disorders</td>
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<td></td>
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<tr>
<td>Anemia</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>17</td>
<td>38</td>
</tr>
</tbody>
</table>

Cosmos Communications 133992a_pi 09.20.16
Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX.

8.1 Pregnancy – Risk Summary: There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from CABOMETYX, advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.2 Lactation – Risk Summary: There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from CABOMETYX, advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

Table 1. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX

Table 3. Clinically Significant Drug Interactions Involving Drugs that Affect Cabozantinib

Strong CYP3A4 Inhibitors

Clinical Implications:

Examples:

Strong CYP3A4 Inducers

Clinical Implications:

Examples:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Risk Summary: Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose. Advise pregnant women or women of childbearing potential of the potential hazard to a fetus.

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

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX

Test

CABOMETYX (n=331)  Everolimus (n=322)  All Grades  Grade 3-4  All Grades  Grade 3-4

Chemistry

Sodium increased 124 4 120 <1

Potassium decreased 25 2 23 1

Creatine kinase increased 29 1 28 1

AST increased 74 3 40 <1

ALT increased 68 3 32 <1

Creatinine increased 59 <1 71 0

Triglycerides increased 53 4 73 13

Hypophosphatemia 48 8 36 5

Hypochloremia 37 2 39 8

Hypocalcemia 36 2 28 <1

ALK increased 35 2 29 1

Hypomagnesemia 31 7 4 <1

Hypotension 30 8 26 6

GOT increased 27 5 43 9

Hematology

White blood cells decreased 35 <1 31 <1

Absolute neutrophil count decreased 31 2 17 <1

Hemoglobin decreased 31 4 71 17

Lymphocytes decreased 25 7 39 12

Platelets decreased 25 <1 27 <1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

8.7 Renal Impairment

Dose adjustment is not required in patients with mild to moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdose was reported in the cabozantinib clinical program; a patient inadvertently took twice the intended dose (200 mg daily) of another formulation of cabozantinib product for nine days. The patient suffered Grade 3 memory impairment, Grade 3 mental state changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage. Gastroesophageal reflux disease (GERD): Advise patients to notify their healthcare provider at the first sign of poorly formed or loose stool or an increased frequency of bowel movements or significant weight loss. Palmar-planar erythrodysesthesia syndrome: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Wound healing: Advise patients to contact their healthcare provider before any planned surgeries, including dental surgery.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medication or herbal products that they are taking.

Embryo-fetal toxicity / Lactation: Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with CABOMETYX and for at least four months after the final dose of CABOMETYX. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with CABOMETYX. Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Important Administration Information

Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Instruct patients to not crush CABOMETYX tablets and to take CABOMETYX tablets with a full glass (at least 8 ounces) of water. Advise patients not to consume grapefruit or grapefruit juice while taking CABOMETYX.
SMA type 0 is the most severe form and occurs before birth. Types 1, 2, and 3 primarily affect infants and children, whereas other types of SMA, including type 4, may affect adolescents and adults. SMA types 1, 2, 3, and 4 are caused by mutations in the survival motor neuron-1 (SMN1) gene, which is one of two genes involved in the production of the survival motor neuron (SMN) protein. The majority of functional SMN protein, which is needed for the maintenance of motor neurons that are responsible for controlling muscle movement, is made by the SMN1 gene. SMN1 gene mutations cause an SMN protein shortage, which results in motor neuron death and reduced neurotransmission between the nervous system and muscles, leading to weakness and impaired movement.

SMA can have a devastating impact on infants, children, and their families, and represents the leading genetic cause of infant mortality. The prognosis for individuals with SMA differs based on subtype, severity, associated symptoms, and response to treatment. For individuals with type 1, the lifespan is generally less than two years, and for individuals with SMA type 2, life expectancy typically does not exceed childhood years.

For those with SMA type 3, life expectancy may extend into adulthood, and for patients with SMA who do not develop symptoms until adulthood, a normal life expectancy may be possible. Presently, there is no cure for SMA; however, the Food and Drug Administration (FDA) recently granted SPINRAZA™ (nusinersen) approval for the treatment of SMA in pediatric and adult patients.

SPINRAZA™ (nusinersen), manufactured by Biogen, is the first drug approved to treat patients with SMA. The FDA granted SPINRAZA™ (nusinersen) Fast Track designation and Priority Review status as well as Orphan Drug designation. The FDA approval of SPINRAZA™ (nusinersen) was based on the results of the pivotal, phase 3 ENDEAR trial (N=121) which evaluated the efficacy of nusinersen in infants who were less than seven months of age at the time of administration of the first dose and had been diagnosed with type 1 SMA prior to six months of age. The primary endpoint of the study was the proportion of responders who demonstrated an improvement in motor milestones. At the time of the interim analysis (N=82), 40% of infants (N=21) treated with nusinersen achieved a motor milestone response, whereas none of the patients in the sham-controlled group demonstrated a motor milestone response (P<0.0001). Additionally, a smaller percentage of patients treated with nusinersen died compared to patients who received placebo (23% vs 43%, respectively).

Although the ENDEAR trial was not statistically controlled for multiple comparisons at the interim analysis, treatment effects were assessed using the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), which is an evaluation of motor skills in patients with infantile-onset SMA. Of the nusinersen-treated patients (N=52), 33 (63%) had at least a 4-point improvement from baseline compared to 1 patient (3%) in the sham-controlled arm. Additionally, 2 patients (4%) in the nusinersen group experienced a worsening of at least 4-points compared to 12 patients (40%) in the sham-controlled group.

The SPINRAZA™ (nusinersen) clinical trial program, which is the largest clinical trial program in SMA to date, consists of multiple sham-controlled and uncontrolled, open-label studies across various populations of patients with SMA, including patients with infantile-onset SMA as well as those who had or were likely to develop (i.e., presymptomatic) type 1, 2, or 3 SMA. The overall findings of the ENDEAR study and additional open-label studies support the effectiveness of SPINRAZA™ (nusinersen) across the range of patients with SMA in which the treatment was studied and may also support early treatment initiation.
The approval of SPINRAZA™ (nusinersen) has not come without criticism, however, as many media outlets have taken issue with the price of treatment which has been set at $750,000 for the first year of treatment and $375,000 for each year of treatment thereafter. In contrast to some other orphan disease therapies, SPINRAZA™ (nusinersen) utilizes one standard dosing regimen across all patients, and this set dosing schedule allows predictability in annual costs on a per-patient basis. Biogen has responded by explaining that the price of SPINRAZA™ (nusinersen) was determined through a rigorous and thoughtful process that evaluated a range of information and strived to achieve an appropriate balance among three key pricing principles – clinical value, impact to the healthcare system, and commitment to patients while advancing science through the funding of research and development. With a potentially transformative ultra-orphan therapy like SPINRAZA™ (nusinersen), the clinical benefit to patients is the cornerstone of the pricing approach.

Biogen performed extensive research to understand the SMA population, including the impact of the disease on patients and families, segmentation of the population by treatment centers and insurance profiles, and potential barriers to treatment such as geographic boundaries. The robust results of this clinical trial program, along with the unmet need within this devastating disease, informed their determination of value, which was validated by primary research that collected direct feedback from payors, healthcare providers, and hospital administrators through blinded interviews. Qualitative and quantitative feedback was collected to gain an understanding of potential access dynamics and the economic impact of the product on various stakeholders. This feedback was supplemented with an analysis of comparable orphan therapies on the market, selected based on a combination of disease prevalence, being first to market, and therapeutic value. Biogen recognizes that access to treatments and affordability are key considerations for patients, providers, payors, and policy makers and have stated that the organization is committed to working with all stakeholders to establish sustainable access for patients that may benefit from SPINRAZA™ (nusinersen).

### Table

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<thead>
<tr>
<th>Trade Name (Manufacturer):</th>
<th>Spinraza (Biogen)</th>
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<tbody>
<tr>
<td>From/Strength:</td>
<td>Single-dose vial; 12 mg/5 mL</td>
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<tr>
<td>FDA Approval/Market Availability:</td>
<td>December 23, 2016; Available</td>
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<tr>
<td>Indication:</td>
<td>Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients</td>
</tr>
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<td>Recommended Dosing:</td>
<td>12 mg intrathecally - Treatment should be initiated with a total of four loading doses: the first three should be administered at 14-day intervals and the fourth loading dose should be administered 30 days after the third loading dose. A maintenance dose should be administered once every four months thereafter</td>
</tr>
<tr>
<td>Place in Therapy:</td>
<td>First and only FDA-approved product for the treatment of SMA.</td>
</tr>
<tr>
<td>Wholesale Acquisition Price (WAC):</td>
<td>$125,000 per 12 mg vial</td>
</tr>
</tbody>
</table>

### References

Discover SPINRAZA™ (nusinersen)

The **FIRST** and **ONLY** FDA-approved treatment for spinal muscular atrophy (SMA) in pediatric and adult patients.¹²

SMA is a rare autosomal recessive neuromuscular disease characterized by motor neuron degeneration that leads to progressive muscle weakness, respiratory problems, and motor function decline.³⁶ SMA is an orphan disease and is a leading genetic cause of infant mortality.⁴

**INDICATION**

SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

**IMPORTANT SAFETY INFORMATION**

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mCL and no patient developed a sustained low platelet count despite continued drug exposure.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney. In a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin Cm were observed in studies with SPINRAZA. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study.

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see adjacent Brief Summary of full Prescribing Information for additional Important Safety Information. For more information please visit www.SPINRAZA.com.

**NOW AVAILABLE**


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1 INDICATIONS AND USAGE

SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage

The recommended dosage is 12 mg (5 mL) per administration.

Initiate SPINRAZA treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose

If a loading dose is delayed or missed, administer SPINRAZA as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

2.2 Important Preparation and Administration Instructions

SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation

• Store SPINRAZA in the carton in a refrigerator until time of use.
• Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use external heat sources.
• Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored.
• Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
• Administer SPINRAZA within 4 hours of removal from vial.

Administration

• Consider sedation as indicated by the clinical condition of the patient.
• Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
• Prior to administration, remove 5 mL of cerebrospinal fluid.
• Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle (see Dosage and Administration (2.1)). Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation.

2.3 Laboratory Testing and Monitoring to Assess Safety

Conduct the following laboratory tests at baseline and prior to each administration of SPINRAZA and as clinically needed (see Warnings and Precautions (5.1, 5.2)):

• Platelet count
• Prothrombin time; activated partial thromboplastin time
• Quantitative spot urine protein testing

3 DOSAGE FORMS AND STRENGTHS

Injection: 12mg/5mL (2.4mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia and Coagulation Abnormalities

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In a clinical study, 6 of 56 (11%) SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal, compared to 0 of 28 sham-procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in this study and no patient developed a sustained low platelet count despite continued drug exposure.

Because of the risk of the thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

5.2 Renal Toxicity

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney (see Clinical Pharmacology (12.3)). In a clinical study (mean treatment exposure 7 months), 17 of 51 (33%) SPINRAZA-treated patients had elevated urine protein, compared to 5 of 25 (20%) sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 36 of 52 (69%) had elevated urine protein. No elevations in serum creatinine or cystatin C were observed in these studies.

Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in detail in other sections of the labeling:

• Thrombocytopenia and Coagulation Abnormalities (see Warnings and Precautions (5.1))
• Renal Toxicity (see Warnings and Precautions (5.2))

6.1 Clinical Trials Experience

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

The data described below reflect exposure to SPINRAZA in 173 patients (50% male, 82% Caucasian), including 120 exposed for at least 6 months and 83 exposed for at least 1 year. The safety of SPINRAZA was studied in infants with symptomatic SMA, approximately 1 month to 8 months of age at study entry; in a sham-controlled trial (n=80 for SPINRAZA, n=41 for control); in open-label studies in presymptomatic and symptomatic infants (n=37), and in open-label studies in later onset patients (n=56, 2 to 15 years of age at study entry). In the controlled study in symptomatic infants, 41 patients were exposed for at least 6 months and 19 patients were exposed for at least 12 months.

In the controlled study, baseline disease characteristics were largely similar in the SPINRAZA treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

In the controlled study, the most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently in control patients were lower respiratory infection, upper respiratory infection, and constipation.

Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study.
Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients in the Controlled Study in Infants with Symptomatic SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg1 N=80%</th>
<th>Sham-Procedure Control N=41%</th>
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<tr>
<td>Lower respiratory infection2</td>
<td>43%</td>
<td>29%</td>
</tr>
<tr>
<td>Upper respiratory infection3</td>
<td>39%</td>
<td>34%</td>
</tr>
<tr>
<td>Constipation</td>
<td>30%</td>
<td>22%</td>
</tr>
<tr>
<td>Teething</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Aspiration</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

1 Four loading doses followed by 12 mg (5 mL) once every 4 months
2 Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia bacterial, bronchitis, bronchitis viral, pneumonia moraxella, pneumonia parainfluenzae viral, lower respiratory tract infection viral, lung infection, pneumonia influenza, pneumonia pseudomonal, pneumonia respiratory syncytial viral
3 Includes upper respiratory tract infection, nasopharyngitis, rhinitis, pharyngitis, or tracheitis

In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months. Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse events in the open-label studies in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%). Most of these events occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with adverse reactions observed in the controlled study.

6.2 Immunogenicity
The immunogenic response to nusinersen was determined in 126 patients with baseline and post baseline plasma samples evaluated for anti-drug antibodies (ADAs). Five (4%) patients developed treatment-emergent ADAs, of which 3 were transient and 2 were considered to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to SPINRAZA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. No adverse effects on embryofetal development were observed in animal studies in which nusinersen was administered by subcutaneous injection to mice and rabbits during pregnancy (see Data).

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

Data
Animal Data
When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

8.2 Lactation
Risk Summary
There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established (see Clinical Studies (14.1)).

Juvenile Animal Toxicity Data
In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use
SMA is largely a disease of children and young adults; therefore, there is no geriatric experience with SPINRAZA.

17 PATIENT COUNSELING INFORMATION
Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs (see Warnings and Precautions (5.1)).

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity (see Warnings and Precautions (5.2)).

Manufactured for:
Biogen Inc.
Cambridge, MA 02142
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<th>Dosage Form</th>
<th>Approval Status</th>
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</table>
The first treatment approved for PBC in nearly 20 years

Discover a First-in-Class Treatment for Primary Biliary Cholangitis

Activate the Power Within

OCALIVA® (obeticholic acid)

Indication
OCALIVA® (obeticholic acid) is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information
Contraindications
OCALIVA is contraindicated in patients with complete biliary obstruction.

Please see Important Safety Information and brief summary of Full Prescribing Information on following pages. Rx only.
Delivered Significant, Sustained Reductions in Alkaline Phosphatase²

### Mean Alkaline Phosphatase Over 12 Months², a

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Placebo + UDCA (n=73)</th>
<th>OCALIVA 5 → 10 mg Titration + UDCA (n=70)</th>
<th>OCALIVA 10 mg + UDCA (n=73)</th>
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<tr>
<td>0</td>
<td>350</td>
<td>325</td>
<td>320</td>
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<tr>
<td>6</td>
<td>325</td>
<td>290</td>
<td>280</td>
</tr>
<tr>
<td>12</td>
<td>300</td>
<td>265</td>
<td>260</td>
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²In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

a ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

### Important Safety Information

#### Warnings and Precautions

#### Liver-Related Adverse Reactions

Dose-related, liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare have been observed in clinical trials, as early as one month after starting treatment with OCALIVA 10 mg once daily up to 50 mg once daily (up to 5-times the highest recommended dosage). Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced serious liver-related adverse reactions. The maximum recommended dosage of OCALIVA is 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment. Discontinue OCALIVA in patients who develop complete biliary obstruction.

#### Severe Pruritus

Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in a 12 month double-blind randomized controlled trial that consisted of 216 patients. Severe pruritus consists of intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. Management strategies include the addition of bile acid resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing.

#### Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high-density lipoprotein-cholesterol (HDL-C). Dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest tolerable, recommended dosage (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.
For patients with PBC who have had an inadequate response for at least 1 year or are intolerant to UDCA

- **OCALIVA** is a farnesoid X receptor (FXR) agonist that works differently than UDCA\(^1,2\)
  - FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways\(^2\)
- 46% of patients taking **OCALIVA** + UDCA met the primary endpoint vs 10% of patients taking UDCA alone\(^2b\)
  - **OCALIVA** is also effective as monotherapy\(^1\) in patients who are intolerant to UDCA
  - Pruritus was the most common adverse event

**Drug Interactions**

- **Bile Acid Binding Resins**
  - Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of **OCALIVA**. If taking a bile acid binding resin, take **OCALIVA** at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

- **Warfarin**
  - The International Normalized Ratio (INR) is decreased following co-administration of warfarin and **OCALIVA**. Monitor INR and adjust the dose of warfarin, as needed, to maintain the target INR range when co-administering **OCALIVA** and warfarin.

- **CYP1A2 Substrates with Narrow Therapeutic Index**
  - Obeticholic acid, the active ingredient in **OCALIVA**, may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline and tizanidine) is recommended when co-administered with **OCALIVA**.

**References:**

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**Your Patients. Our Commitment.**

From enrollment to insurance—including our $0 co-pay program\(^4\)—Interconnect provides support to assist your office and help your patients start and stay on **OCALIVA**. Visit [interconnectsupport.com](http://www.interconnectsupport.com) or call 1-844-622-ICPT to get your patients started.

\(^4\)For patients with commercial insurance.

Want to learn more about how to take PBC treatment further with **OCALIVA**?
Please visit [ocalivahcp.com](http://www.ocalivahcp.com).

To learn more about Intercept Pharmaceuticals, Inc., please visit [interceptpharma.com](http://www.interceptpharma.com).

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**Adverse Reactions**

The most common adverse reactions from subjects taking **OCALIVA** (≥5%) were pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema.

**Drug Interactions**

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Brief Summary of Prescribing Information for OCALIVA® (obeticholic acid) OCALIVA (obeticholic acid) tablets, for oral use

See package insert for Full Prescribing Information.

INDICATIONS AND USAGE: OCALIVA is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with moderate or severe hepatic impairment, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP) [see Clinical Studies (14) in Full Prescribing Information]. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS: OCALIVA is contraindicated in patients with complete biliary obstruction. WARNINGS AND PRECAUTIONS: Liver-Related Adverse Reactions: In two 3-month, placebo-controlled trials, a dose-related relationship was observed in the occurrence of liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5 times the highest recommended dosage), as early as one month after starting treatment with OCALIVA [see dose and administration (2.1) in Full Prescribing Information]. Advise the dosage for patients with moderate or severe hepatic impairment [see dose and administration (2.3) in Full Prescribing Information]. Discontinue OCALIVA in patients who develop complete biliary obstruction [see Contraindications]. Severe Pruritus: Severe pruritus was reported in 29% of patients in the OCALIVA titration arm and 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in Trial 1, a 12-month double-blind randomized controlled trial of 216 patients [see Adverse Reactions]. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe distress, intolerance, or intense discomfort, and typically requiring medical interventions. In the subgroup of patients in the OCALIVA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 6-12 and 15% from Months 6-12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively. Management strategies include the addition of bile acid resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing [see Warnings and Precautions]. Reduction in HDL-C: Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). In Trial 1, dose-dependent reductions in HDL-C were observed at all 3 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At month 12, the reduction from baseline in mean HDL-C level was 19% in the OCALIVA 10 mg arm, 12% in the OCALIVA titration arm, and 2% in the placebo arm. Nine patients in the OCALIVA titration arm, two patients in the titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment. ADVERSE REACTIONS: The following clinically significant adverse reactions are described elsewhere in labeling: • Liver-Related Adverse Reactions [see Warnings and Precautions] • Severe Pruritus [see Warnings and Precautions] • Reduction in HDL-C [see Clinical Trials Experience] • Laboratory Abnormalities [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The overall incidence rate of adverse reactions in two 3-month, placebo-controlled trials of 322 patients with PBC who were randomized (1:1:1) to receive each: • OCALIVA 10 mg once daily for the entire 12 months of the trial (n=73); • OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months) (n=74); or were tolerating UDCA 5 mg once daily in Trial 1, and were randomized to receive: • placebo (n=70). During the trial, OCALIVA or placebo was administered in combination with UDCA in 93% of patients and as monotherapy in 7% of patients who were unable to tolerate UDCA. The overall discontinuation rate was 12% in the OCALIVA 10 mg arm, 10% in the OCALIVA titration arm, and 4% in the placebo arm. The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response [see Dosage and Administration (2.1) in Full Prescribing Information]. Initiation of therapy with OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus. The most common adverse reactions in Trial 1 occurring in at least 5% of patients in the OCALIVA titration arm and at an incidence at least 1% higher than the placebo treatment arm are shown in Table 1.

Table 1: Most Common Adverse Reactions in Adult Patients with PBC in Trial 1 by Treatment Arm with or without UDCA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OCALIVA 10 mg</th>
<th>OCALIVA Titration</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 73</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>70</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain and discomfort</td>
<td>10</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Rectal pain</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid function abnormality</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Eczema</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

a In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

b Occurring in greater than or equal to 5% of patients in either OCALIVA treatment arm and at an incidence greater than or equal to 1% higher in the placebo treatment arm.

c Patients randomized to OCALIVA titration received OCALIVA 5 mg once daily for the initial 6 month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

d Includes skin eruptions, prurigo, pruritus, pruritus generalized, eye pruritus, ear pruritus, anal pruritus, vulvovaginal pruritus, and rash pruritic.

e Includes fatigue, tiredness and asthenia.

f Includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

g Includes urticaria, rash, rash macular, rash papular, rash maculo-papular, heat rash, urticaria choleteric.

h Includes dizziness, syncope, presyncope.

i Includes thyroid function abnormality.

j Includes thyroxine free decreased, blood thyroid stimulating hormone increased, hypothyroidism.

Liver-Related Adverse Reactions: In Trial 1, the following serious or otherwise clinically significant liver-related adverse reactions were reported at the recommended dosage of OCALIVA: one patient in the OCALIVA 10 mg treatment arm was hospitalized; one patient in the OCALIVA titration treatment arm experienced two episodes of ascites and four episodes of hepatic encephalopathy; one patient in the placebo treatment arm experienced variceal bleeding. Pruritus: Approximately 80% of patients had a history of pruritus upon enrollment in Trial 1. Treatment-emergent pruritus, including all the terms described in Table 1, generally started within the first month following the initiation of treatment with OCALIVA. The incidence of pruritus was higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 70% and 56%, respectively. Discontinuation rates due to pruritus were higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 10% and 1%, respectively. The number of patients with pruritus who required an intervention (e.g., dosage adjustment, treatment interruption, or initiation of bile acid binding resin or antihistamine) was 30 of 51 patients (59%) in the OHALA titration arm, and 14 of 28 patients (50%) in the placebo arm. DRUG INTERACTIONS: Bile Acid Binding Resins: Bile acid binding resins such as cholestyramine, colestipol, or colesvelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible [see Dosage and Administration (2.4) in Full Prescribing Information]. Warfarin: The International Normalized Ratio (INR) decreased following coadministration of warfarin and OCALIVA [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.

CYP1A2 Substrates with Narrow Therapeutic Index: Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates
was administered in combination with UDCA in 93% of patients and as a single agent in 7%. In patients who were tolerating OCALIVA, but had ALP 1.67-times the upper limit of normal, the bile acid binding resin was administered orally during the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13 times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40 times the human exposure at the MRHD), decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight, and food consumption as well as decreased body weight gain were observed at 75 mg/kg/day. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic acid administered at doses up to 20 mg/kg/day (approximately 6 times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm. In a pre- and postnatal developmental study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition or postnatal development at any dose (the 40 mg/kg/day dose is approximately 21 times the human exposure at the MRHD). Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid’s active metabolite conjugates (tauro-obeticholic acid and glyco-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg.

**Lactation:** Risk Summary: There is no information on the presence of obeticholic acid in human milk. The effects on the breast-fed infant or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for OCALIVA and any potential adverse effects on the breast-fed infant from OCALIVA or from the underlying maternal condition. **Pediatric Use:** The safety and effectiveness of OCALIVA in pediatric patients have not been established. **Geriatric Use:** Of the 201 patients in clinical trials of OCALIVA who received the recommended dosage (5 mg or 10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C) [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions [see Warnings and Precautions]. Dosage adjustment of OCALIVA is recommended for patients with moderate and severe hepatic impairment [see Dosage and Administration (2.3) in Full Prescribing Information]. No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A).

**OVERDOSAGE:** In PBC patients who received OCALIVA 25 mg once daily (2.5 times the highest recommended dosage) or 50 mg once daily (5 times the highest recommended dosage), a dose-dependent increase in the incidence of liver-related adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flare, was reported [see Warnings and Precautions]. In the case of overdosage, patients should be carefully observed and supportive care administered, as appropriate.

**PATIENT COUNSELING INFORMATION:** Liver-Related Adverse Reactions: • Advise patients to report any symptoms of worsening of liver disease to their healthcare provider immediately and that they may need to undergo laboratory testing periodically while on OCALIVA treatment to assess liver function [see Warnings and Precautions]. • Advise patients who develop symptoms of complete biliary obstruction to report to their healthcare provider immediately [see Contraindications]. Severe Pruritus: • Advise patients to contact their healthcare provider if they experience pruritus or an increase in the severity of pruritus [see Warnings and Precautions]. Reduction in HDL-C: • Advise patients that they may need to undergo laboratory testing to check for changes in lipid levels while on treatment with OCALIVA [see Warnings and Precautions]. Administration: Advise patients to take: • OCALIVA with or without food. • OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or as at great an interval as possible [see Drug Interactions].

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From 2014 to 2015, the increase in net cost per claim was $1.26, which represents a year-over-year 3% increase, and the increase in gross cost per claim was $9.17, which represents a 10.7% increase. The trend of accelerating drug prices was mitigated by the use of strategies such as preferred drug lists (PDLs), utilization management (UM), clinical criteria, and brand-over-generic opportunities, all of which helped to minimize the increase in net cost per claim.

As expected, federal and supplemental rebates largely contributed to the lower net cost of pharmacy expenditures, as well as selection of brand-over-generic preferences.

• State laws that restrict or limit a state’s ability to manage specific therapeutic classes had a significant influence in determining the overall cost effectiveness of a pharmacy program.

Additionally, the report includes a prospective analysis and provides recommendations of strategies that the FFS pharmacy programs in each state should consider implementing to optimize patient health and cost savings. Magellan Rx Management recommends that states implement the following strategies to enhance Medicaid pharmacy savings opportunities:

• Complemented with appropriate clinical criteria, states should examine practices around PDL restrictions of certain classes.

Based on federal and supplemental rebates available to Medicaid programs, states should use the resulting net cost of drugs as a basis for making decisions around the formulary inclusion.

• To provide enhanced cost savings, states should consider supplemental rebate negotiation and evaluation and net cost monitoring. Of note, supplemental rebate negotiation and evaluation resulted in savings exceeding $1.3 billion for states from 2014 through 2015, and a preferred brand-over-generic strategy achieved $86 million in savings in the fourth quarter of 2015 alone.

A full copy of the 28-page report can be downloaded by visiting the Magellan Rx Management website and can be found under the Publications tab.


REFERENCES
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Over the last half-century, we have brought together a family of innovative pharmaceutical companies all with one overarching mission: to address and solve some of the most important unmet medical needs of our time.

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Janssen is proud to feature artwork created by people affected by the illnesses and diseases we are committed to treating and preventing.