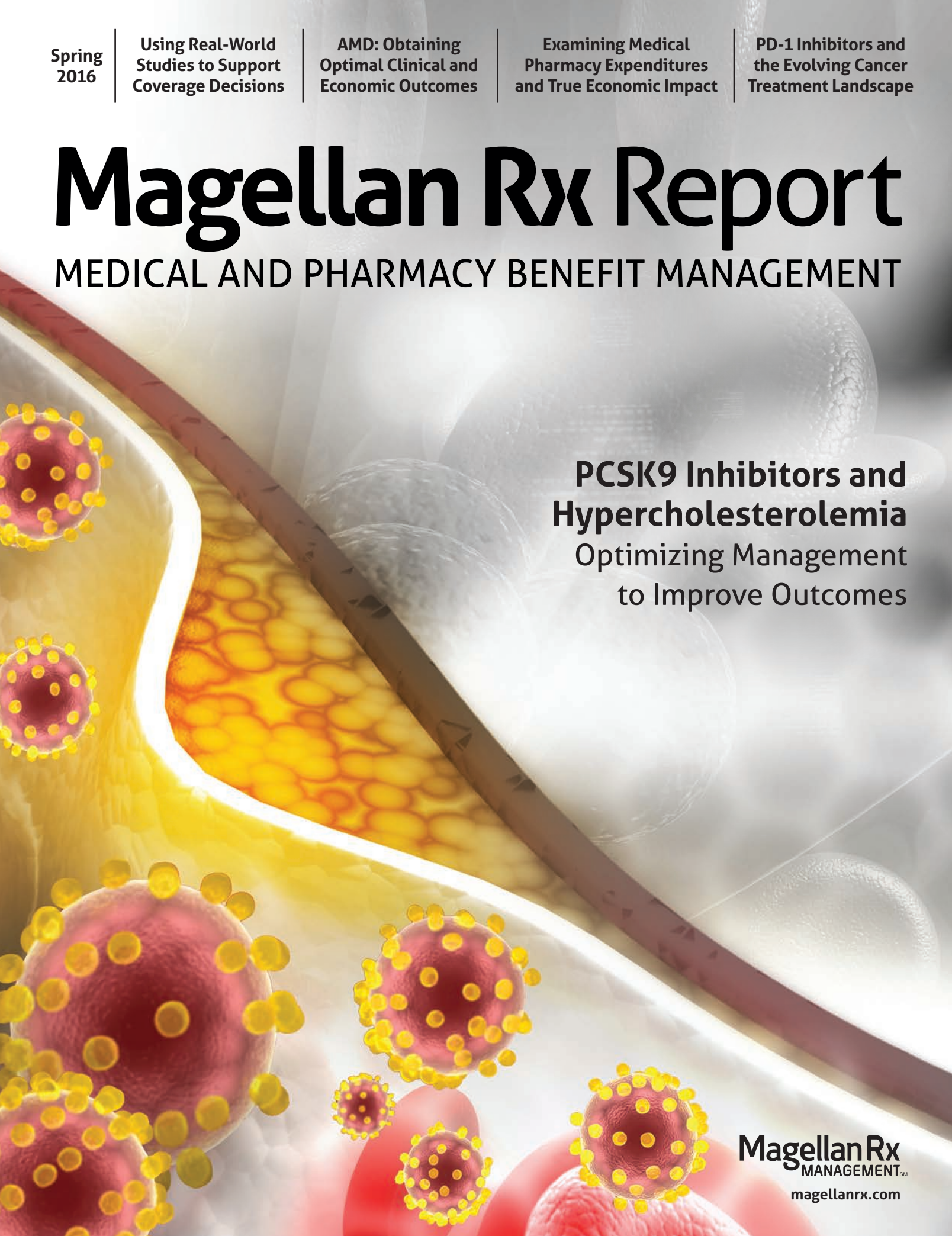
Spring 2016

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT



PCSK9 Inhibitors and Hypercholesterolemia

Optimizing Management to Improve Outcomes

Magellan Rx MANAGEMENT℠

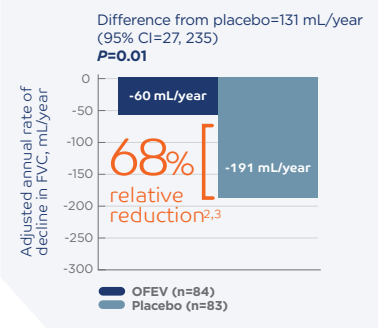
magellanrx.com

OFEV (nintedanib) is now recommended for the treatment of idiopathic pulmonary fibrosis (IPF) in the 2015 ATS/ERS/JRS/ALAT Clinical Practice Guideline[1*†]

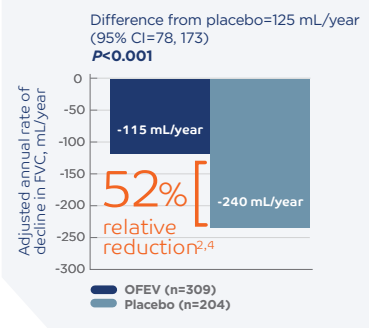
Slow the Path of IPF Progression for Your Members

OFEV demonstrated reproducible reductions in the annual rate of FVC decline‡ in 3 clinical trials[2]

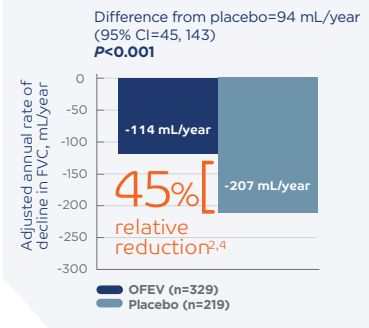
TOMORROW (Study 1)[2,3]



INPULSIS®-1 (Study 2)[2,4]



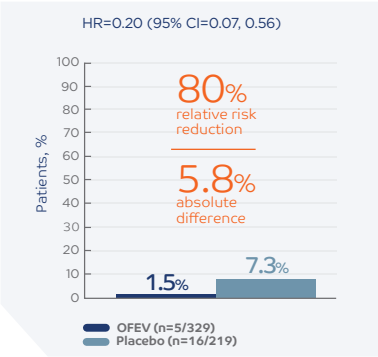
INPULSIS®-2 (Study 3)[2,4]



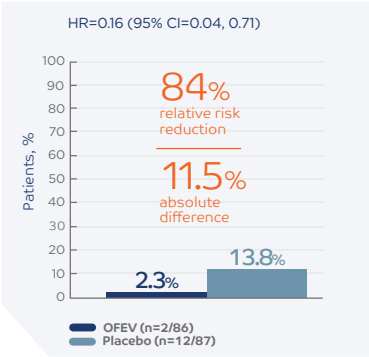
CI, confidence interval; FVC, forced vital capacity.
*Conditional recommendation for use; moderate confidence in effect estimates.[1]
†ATS, American Thoracic Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Association.
‡The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.[2,4]

OFEV significantly reduced the risk of time to first acute IPF exacerbation in 2 out of 3 clinical trials[2§]

INPULSIS®-2 (adjudicated)[2,5]



TOMORROW (investigator-reported)[2,5]



In INPULSIS©-1 (adjudicated), there was no difference in treatment groups (HR=0.55, 95% CI=0.20, 1.54).[2]

The effect of OFEV on the annual rate of FVC decline and time to first acute IPF exacerbation indicates a slowing of disease progression[2,6-9]

HR, hazard ratio
§Diagnostic criteria for acute IPF exacerbations were prespecified in the trial protocol as events meeting all of the following criteria: unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest X-radiography and/or HRCT, or new parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit, exclusion of infection (as per routine clinical practice and microbiological studies), and exclusion of alternative causes (as per routine clinical practice and including the following: left heart failure, pulmonary embolism, and identifiable cause of acute lung injury).[2,4]

INDICATION AND USAGE

OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

- The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment.
- In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
- Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients.
- Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Gastrointestinal Disorders (cont'd)

Nausea and Vomiting

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients.
- For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV.

Embryofetal Toxicity

- OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

Arterial Thromboembolic Events

- Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding

- Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation

- Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with OFEV and more commonly than in patients treated with placebo included diarrhea (62% vs. 18%), nausea (24% vs.7%), abdominal pain (15% vs 6%), liver enzyme elevation (14% vs 3%), vomiting (12% vs 3%), decreased appetite (11% vs 5%), weight decreased (10% vs 3%), headache (8% vs 5%), and hypertension (5% vs 4%).
- The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients.

DRUG INTERACTIONS

P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers

- Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

Anticoagulants

- Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

Nursing Mothers

- Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic Impairment

- Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment (Child Pugh A). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended.

Smokers

- Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OFHCPISIJAN15

References: 1. Raghu G et al; on behalf of ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192(2):e3–e19. **2.** OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. **3.** Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*. 2011;365(12):1079-1087. **4.** Richeldi L, du Bois RM, Raghu G, et al; for the INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082. **5.** Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **6.** Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;35(4):830-836. **7.** Schmidt SL, Tayob N, Han MK, et al. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. *Chest*. 2014;145(3):579-585. **8.** du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. **9.** Song JW, Hong S-B, Lim C-M, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J*. 2011;37(2):356-363.

OFEV® (nintedanib) capsules 150mg

Please see accompanying full Prescribing Information, including Patient Information.

Boehringer Ingelheim

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests prior to initiating treatment with OFEV *[see Warnings and Precautions]*. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. **Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions and Adverse Reactions]*. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions and Adverse Reactions]*. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment *[see Use in Specific Populations]*. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN *[see Use in Specific Populations]*. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders:** Diarrhea: Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions)]*. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV (nintedanib). Nausea and Vomiting: Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV *[see Use in Specific Populations]*. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations *[see Warnings and Precautions];* Gastrointestinal Disorders *[see Warnings and Precautions];* Embryofetal Toxicity *[see Warnings and Precautions];* Arterial Thromboembolic Events *[see Warnings and Precautions];* Risk of Bleeding *[see Warnings and Precautions];* Gastrointestinal Perforation *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV (nintedanib), more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous systemic disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exp sure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust

anticoagulation treatment as necessary *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category D. [See Warnings and Precautions]:* OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended *[see Warnings and Precautions]*. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: *Advise the patient to read the FDA-approved patient labeling (Patient Information).* Liver Enzyme and Bilirubin Elevations: Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*. Gastrointestinal Disorders: Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting *[see Warnings and Precautions and Adverse Reactions]*. Pregnancy: Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV *[see Warnings and Precautions and Use in Specific Populations]*. Arterial Thromboembolic Events: Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions]*. Risk of Bleeding: Bleeding events have been reported. Advise patients to report unusual bleeding *[see Warnings and Precautions]*. Gastrointestinal Perforation: Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions]*. Nursing Mothers: Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing *[see Use in Specific Populations]*. Smokers: Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. Administration: Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration]*.

OF-BS-10-14 (10-15) OF629900PROF

℞ only

Boehringer Ingelheim

Magellan Rx MANAGEMENT℠

Get it from the Source

Now in its sixth edition, the Magellan Rx Management Medical Pharmacy Trend Report™ is the nation's source for trends and dynamics impacting the medical benefit drug landscape in 2015.

Download your complimentary copy today at magellanrx.com!

Welcome to the **Magellan Rx** Report

Published By

Magellan Rx Management
15950 North 76th Street
Scottsdale, AZ 85260

Tel: 401-344-1000
Fax: 401-619-5215

MagellanRxReport@magellanhealth.com
magellanrx.com

Publishing Staff

Todd C. Lord, PharmD, AE-C, CDOE
Themmi Evangelatos, PharmD, MSBA
Carolyn Farnum, BS
Steve D. Cutts, PharmD, AE-C, CDOE
Haita Makanji, PharmD
Sagar Makanji, PharmD

Advertising and Sales

Joe Tavares
401-344-1034
JTavares@magellanhealth.com

ISSN: 2159-5372 10444M

Features

Trends

Mostafa Kamal

Dear Managed Care Colleagues,

I would like to take this opportunity to share some exciting news about key innovations taking place at Magellan that we expect will transform oncology management within the managed care industry. As many of you already know, Magellan Health has been developing innovative solutions for our payor, employer, and government clients since 1969. Our unique business model has allowed Magellan to become a leader in behavioral health, specialty health solutions such as cardiovascular, pain management, and imaging services, as well as comprehensive pharmacy management including specialty drug management on both the pharmacy and medical benefits. At Magellan, we firmly believe that new and innovative solutions must be constantly explored in order to respond to a rapidly changing health care environment.

To meet the evolving needs of our clients, Magellan has identified key areas of focus where we have integrated our best-in-class capabilities and expertise across the broader Magellan enterprise to create a number of solutions under our "One Magellan" banner. One of the primary areas of focus for our One Magellan initiative is to develop innovative solutions around oncology management. The challenges and complexities of oncology management are no secret to our managed care colleagues, and containing cost while ensuring appropriate access to medical services and pharmaceutical products has been difficult.

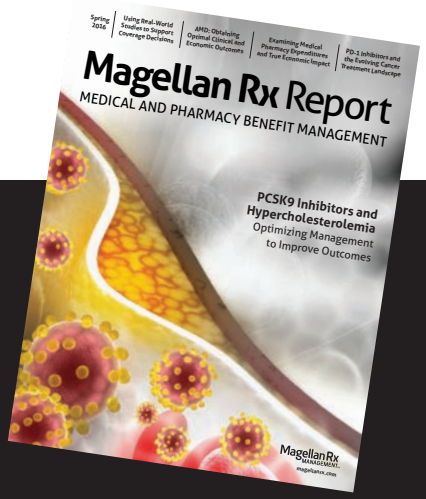
To help overcome these challenges, Magellan has leveraged our experience across all segments of our business and developed comprehensive solutions for appropriate oncology management. These solutions allow integration between medical oncology, pharmacy services, radiation therapy, genetic testing and imaging, cognitive behavioral therapy, caregiver support, and end-of-life care.

Magellan Rx Management is always looking for new and innovative strategies to improve quality of care and contain costs for our health plan, employer, and government clients. Combining our collective scale and experience uniquely positions Magellan to provide industry-leading oncology management solutions designed to improve outcomes and the overall member experience, while ensuring a clear focus on the specific clinical and financial objectives of each individual customer.

To learn more about our One Magellan initiatives or for more information on our oncology solutions, 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



SUBSCRIBE TODAY!

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.

WHEN CHOOSING A NOAC, IT'S TIME TO

ENTER THE WORLD OF

Please see Important Safety Information, including **Boxed WARNINGS**, and brief summary of Full Prescribing Information on following pages.

NOAC=novel oral anticoagulant.

For stroke risk reduction in NVAF patients with CrCl ≤95 mL/min

GIVE THEM THE **ONLY** ONCE-DAILY NOAC THAT OFFERS

SUPERIORITY WITH LESS MAJOR BLEEDING

INDICATION

SAVAYSA® (edoxaban) is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF). SAVAYSA should not be used in patients with creatinine clearance (CrCl) >95 mL/min because of an increased risk of ischemic stroke compared to warfarin.

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

- **REDUCED EFFICACY IN NVAF PATIENTS WITH CRCL >95 ML/MIN**
  SAVAYSA should not be used in patients with CrCl >95 mL/min. In the ENGAGE AF-TIMI 48 study, NVAF patients with CrCl >95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used
- **PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS**
  Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance in the Prescribing Information
- **SPINAL/EPIDURAL HEMATOMA**
  - **Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures**

WARNINGS AND PRECAUTIONS

Bleeding Risk

- SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss. Discontinue SAVAYSA in patients with active pathological bleeding. Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of nonsteroidal anti-inflammatory drugs. There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse its anticoagulant activity

Please see additional Important Safety Information, including **Boxed WARNINGS**, on next page and brief summary of Full Prescribing Information on following pages.

REDUCED RISK OF STROKE/SE VS WELL-MANAGED WARFARIN

PRESCRIBE SAVAYSA, THE ONLY ONCE-DAILY NOAC THAT OFFERS A COMBINATION OF:

Superiority to warfarin with less major bleeding[1]*

16% relative risk reduction (RRR): 3.1%/year with SAVAYSA vs 3.7%/year with warfarin (HR [95% CI]: 0.84 [0.73-0.97])

Reduced risk of stroke/SE† vs well-managed warfarin (mean TTR: 65%) in a high-risk population (mean $CHADS_2$ score: 2.8‡)[1,2]

32% RRR in stroke/SE: 1.2%/year with SAVAYSA vs 1.8%/year with warfarin (HR [95% CI]: 0.68 [0.55-0.84])

18% RRR in CV death: 2.95%/year with SAVAYSA vs 3.59%/year with warfarin (HR [95% CI]: 0.82 [0.72-0.93])

Convenient once-daily dosing[1]

Can be taken with or without food

- No dose adjustment with P-gp or CYP450 inhibitors for NVAF patients

ENGAGE AF-TIMI 48 STUDY DESIGN[1,2]

The ENGAGE AF-TIMI 48 study was a multinational, randomized, double-blind, noninferiority study comparing the efficacy and safety of SAVAYSA (N=7012) and warfarin (N=7012) in NVAF patients with $CHADS_2$ ≥2. The median treatment duration was 2.5 years and the median age was 72 years. Approximately 77% of the patients in the study had CrCl ≤95 mL/min (N=5417 for SAVAYSA, N=5485 for warfarin).

NOAC=novel oral anticoagulant; TTR=time in therapeutic range (International Normalized Ratio [INR] target 2.0 to 3.0); P-gp=P-glycoprotein.

*The primary safety endpoint was major bleeding that occurred during or within 2 days of stopping study treatment. Major bleeding was defined as clinically overt bleeding that met 1 of the following criteria: fatal bleeding, symptomatic bleeding in critical area/organ, caused a fall in hemoglobin of at least 2.0 g/dL (or a fall in hematocrit of at least 6.0%), when adjusted for transfusions (1 unit of transfusion=1.0 g/dL drop in hemoglobin).[1]

†The primary efficacy endpoint of the study was the occurrence of first stroke (either ischemic or hemorrhagic) or systemic embolism (SE).[1]

‡Scores on the $CHADS_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or transient ischemic attack is assigned 2 points.[2]

once-daily
Savaysa®
(edoxaban) tablets
60mg/30mg

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

- **REDUCED EFFICACY IN NVAF PATIENTS WITH CRCL >95 ML/MIN**
  SAVAYSA should not be used in patients with CrCl >95 mL/min. In the ENGAGE AF-TIMI 48 study, NVAF patients with CrCl >95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used
- **PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS**
  Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance in the Prescribing Information
- **SPINAL/EPIDURAL HEMATOMA**
  - **Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures**
  - **Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; a history of spinal deformity or spinal surgery**
  - **Optimal timing between the administration of SAVAYSA and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- SAVAYSA is contraindicated in patients with active pathological bleeding

WARNINGS AND PRECAUTIONS

Bleeding Risk

- SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss. Discontinue SAVAYSA in patients with active pathological bleeding. Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of nonsteroidal anti-inflammatory drugs. There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse its anticoagulant activity

Mechanical Heart Valves or Moderate to Severe Mitral Stenosis

- The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. SAVAYSA is not recommended in these patients

ADVERSE REACTIONS

- The most common adverse reactions (≥5%) are bleeding and anemia

DISCONTINUATION FOR SURGERY AND OTHER INTERVENTIONS

- Discontinue SAVAYSA at least 24 hours before invasive or surgical procedures because of the risk of bleeding. SAVAYSA can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established

DRUG INTERACTIONS

- **Anticoagulants, Antiplatelets, and Thrombolytics:** Coadministration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding
- **P-gp Inducers:** Avoid concomitant use of SAVAYSA with rifampin

SPECIAL POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing
- Impaired renal function (CrCl 15 to 50 mL/min): Reduce SAVAYSA dose to 30 mg once daily
- Moderate or severe hepatic impairment: Not recommended
- Pregnancy Category C

Please see brief summary of Full Prescribing Information on following pages.

References: 1. SAVAYSA® [package insert], Parsippany, NJ: Daiichi Sankyo, Inc; 2015. **2.** Giugliano RP, Ruff CT, Braunwald E, et al; for ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104.

once-daily Savaysa® (edoxaban) tablets 60mg/30mg

Daiichi-Sankyo

DSSV15000186 07/15

SAVAYSA™ (edoxaban) tablets for oral use
Initial U.S. Approval: 2015

BRIEF SUMMARY: See package insert for full prescribing information.

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN (B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS (C) SPINAL/EPIDURAL HEMATOMA

A. REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1) in the full prescribing information]*.

B. PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance *[see Dosage and Administration (2.4), Warnings and Precautions (5.2), and Clinical Studies (14.1) in the full prescribing information]*.

C. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of SAVAYSA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.4)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.4)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

1.1 Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

SAVAYSA is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF).

Limitation of Use for NVAF

SAVAYSA should not be used in patients with CrCL > 95 mL/min because of an increased risk of ischemic stroke compared to warfarin *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), Clinical Studies (14.1) in the full prescribing information]*.

1.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.

4 CONTRAINDICATIONS

SAVAYSA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Reduced Efficacy in Nonvalvular Atrial Fibrillation Patients with CrCL > 95 mL/min

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the randomized ENGAGE AF-TIMI 48 study, NVAF patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg daily compared to patients treated with warfarin. In these patients another anticoagulant should be used *[see Dosage and Administration (2.1)*, *Clinical Studies (14.1) in the full prescribing information]*.

5.2 Increased Risk of Stroke with Discontinuation of SAVAYSA in Patients with Nonvalvular Atrial Fibrillation

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in the full prescribing information]*.

5.3 Risk of Bleeding

SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss.

Discontinue SAVAYSA in patients with active pathological bleeding.

Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.1)]*.

There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of SAVAYSA.

5.4 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of SAVAYSA. The next dose of SAVAYSA should not be administered earlier than 2 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.5 Patients with Mechanical Heart Valves or Moderate to Severe Mitral Stenosis

The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. The use of SAVAYSA is not recommended in these patients *[see Clinical Studies (14.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of stroke with discontinuation of SAVAYSA in patients with NVAF *[see Warnings and Precautions (5.2)]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions (5.4)]*

The most serious adverse reactions reported with SAVAYSA were related to bleeding *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

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

The safety of SAVAYSA was evaluated in the ENGAGE AF-TIMI 48 and Hokusai VTE studies including 11,130 patients exposed to SAVAYSA 60 mg and 7002 patients exposed to SAVAYSA 30 mg once daily *[see Clinical Studies (14) in the full prescribing information]*.

The ENGAGE AF-TIMI 48 Study

In the ENGAGE AF-TIMI 48 study, the median study drug exposure for the SAVAYSA and warfarin treatment groups was 2.5 years.

Bleeding was the most common reason for treatment discontinuation. Bleeding led to treatment discontinuation in 3.9% and 4.1% of patients in the SAVAYSA 60 mg and warfarin treatment groups, respectively.

In the overall population, Major Bleeding was lower in the SAVAYSA group compared to the warfarin group [HR 0.80 (0.70, 0.91), p<0.001]. Table 6.1 shows Major Bleeding events (percentage of patients with at least one bleeding event, per year) for the indicated population (CrCL ≤ 95 mL/min).

Table 6.1: Adjudicated Bleeding Events for NVAF Patients with CrCL ≤ 95 mL/min*

Event[a]	SAVAYSA 60 mg[b] N = 5417 n (%/year)	Warfarin N = 5485 n (%/year)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
Major Bleeding[c]	357 (3.1)	431 (3.7)	0.84 (0.73, 0.97)
Intracranial Hemorrhage (ICH)[d]	53 (0.5)	122 (1.0)	0.44 (0.32, 0.61)
Hemorrhagic Stroke	33 (0.3)	69 (0.6)	0.49 (0.32, 0.74)
Other ICH	20 (0.2)	55 (0.5)	0.37 (0.22, 0.62)
Gastrointestinal	205 (1.8)	150 (1.3)	1.40 (1.13, 1.73)
Fatal Bleeding	21 (0.2)	42 (0.4)	0.51 (0.30, 0.86)
ICH	19 (0.2)	36 (0.3)	0.54 (0.31, 0.94)
Non-intracranial	2 (<0.1)	6 (<0.1)	----
CRNM Bleeding[e]	982 (9.4)	1132 (10.9)	0.87 (0.80, 0.95)

Abbreviations: HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, n = number of patients with events, N = number of patients in Safety population, CRNM = Clinically Relevant Non-Major.

* During or within 2 days of stopping study treatment

[a] A subject can be included in multiple sub-categories if he/she had an event for those categories.

[b] Includes all patients with CrCL ≤ 95 mL/min randomized to receive 60 mg once daily, including those who were dose-reduced to 30 mg once daily because of prespecified baseline conditions.

[c] A Major Bleeding event (the study primary safety endpoint) was defined as clinically overt bleeding that met one of the following criteria: fatal bleeding; symptomatic bleeding in a critical site such as retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome; a clinically overt bleeding event that caused a fall in hemoglobin of at least 2.0 g/dL (or a fall in hematocrit of at least 6.0% in the absence of hemoglobin data), when adjusted for transfusions (1 unit of transfusion = 1.0 g/dL drop in hemoglobin).

[d] ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epidural/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion.

[e] A Clinically Relevant Non-Major bleeding event was defined as an overt bleeding event that required medical attention, including those that may have resulted in diagnostic or therapeutic measures.

The most common site of a Major Bleeding event was the gastrointestinal (GI) tract. Table 6.2 shows the number of and the rate at which patients experienced GI bleeding in the SAVAYSA 60 mg and warfarin treatment groups.

Table 6.2: Gastrointestinal Bleeding Events for NVAF Patients with CrCL ≤ 95 mL/min*

	SAVAYSA N= 5417 n (%/year)	Warfarin N= 5485 n (%/year)
Major Gastrointestinal (GI) Bleeding[a]	205 (1.78)	150 (1.27)
- Upper GI	123 (1.06)	88 (0.74)
- Lower GI[b]	85 (0.73)	64 (0.54)
GUSTO[c] Severe GI bleeding	16 (0.14)	17 (0.14)
Fatal GI bleeding	1 (<0.1)	2 (<0.1)

* During or within 2 days of stopping study treatment

[a] GI bleeding was defined by location as upper or lower GI

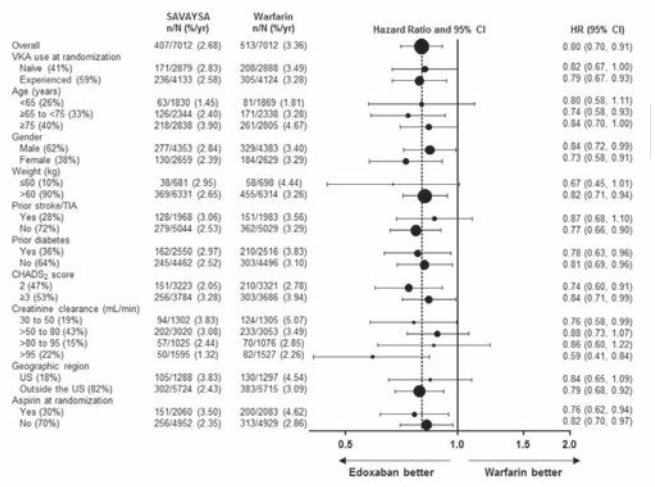
[b] Lower GI bleeding included anorectal bleeding

[c] GUSTO – Severe or life-threatening bleeding that caused hemodynamic compromise and requires intervention

The rate of anemia-related adverse events was greater with SAVAYSA 60 mg than with warfarin (9.6% vs. 6.8%).

The comparative rates of Major Bleeding on SAVAYSA and warfarin were generally consistent among subgroups (see Figure 6.1). Bleeding rates appeared higher in both treatment arms (SAVAYSA and warfarin) in the following subgroups of patients: those receiving aspirin, those in the United States, those more than 75 years old and those with reduced renal function.

Figure 6.1: Adjudicated Major Bleeding in the ENGAGE AF-TIMI 48* Study



*During or within 2 days of stopping study treatment

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Other Adverse Reactions

The most common non-bleeding adverse reactions (≥ 1%) for SAVAYSA 60 mg versus warfarin were rash (4.2% vs. 4.1%), and abnormal liver function tests (4.8% vs. 4.6%), respectively.

Interstitial Lung Disease (ILD) was reported as a serious adverse event on treatment for SAVAYSA 60 mg and warfarin in 15 (0.2%) and 7 (0.1%) patients, respectively. Many of the cases in both treatment groups were confounded by the use of amiodarone, which has been associated with ILD, or by infectious pneumonia. In the overall study period, there were 5 and 0 fatal ILD cases in the SAVAYSA 60 mg and warfarin groups, respectively.

The Hokusai VTE Study

In the Hokusai VTE study, the duration of drug exposure for SAVAYSA was ≤ 6 months for 1561 (37.9%) of patients, > 6 months for 2557 (62.1%) of patients and 12 months for 1661 (40.3%) of patients.

Bleeding was the most common reason for treatment discontinuation and occurred in 1.4% and 1.4% of patients in the SAVAYSA and warfarin arms, respectively.

Bleeding in Patients with DVT and/or PE in the Hokusai VTE Study

The primary safety endpoint was Clinically Relevant Bleeding, defined as the composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding that occurred during or within three days of stopping study treatment. The incidence of Clinically Relevant Bleeding was lower in SAVAYSA than warfarin [HR (95% CI): 0.81 (0.71, 0.94); p =0.004].

Table 6.3 shows the number of patients experiencing bleeding events in the Hokusai VTE Study.

Table 6.3: Bleeding Events in the Hokusai VTE Study

	SAVAYSA (N=4118)	**Warfarin (N=4122)**
Clinically Relevant Bleeding[a] (Major/CRNM), n (%)	349 (8.5)	423 (10.3)
Major Bleeding[b], n (%)	56 (1.4)	66 (1.6)
Fatal bleeding	2 (<0.1)	10 (0.2)
Intracranial fatal	0 (0.0)	6 (0.1)
Non-fatal critical organ bleeding	13 (0.3)	25 (0.6)
Intracranial bleeding	5 (0.1)	12 (0.3)
Non-fatal non-critical organ bleeding	41 (1.0)	33 (0.8)

(continued)

Table 6.3: Bleeding Events in the Hokusai VTE Study

	SAVAYSA (N=4118)	Warfarin (N=4122)
Decrease in Hb ≥ 2g/dL	40 (1.0)	33 (0.8)
Transfusion of ≥ 2 units of RBC	28 (0.7)	22 (0.5)
CRNM Bleeding[c]	298 (7.2)	368 (8.9)
Any Bleed	895 (21.7)	1056 (25.6)

Abbreviations: N=number of patients in the modified intent-to-treat population; n = number of events; CRNM = clinically relevant non-major

[a] Primary Safety Endpoint: Clinically Relevant Bleeding (composite of Major and CRNM).

[b] A Major Bleeding event was defined as clinically overt bleeding that met one of the following criteria: associated with a fall in hemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of packed red cells or whole blood; occurring in a critical site or organ: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; contributing to death.

[c] CRNM bleeding was defined as overt bleeding not meeting the criteria for a Major Bleeding event but that was associated with a medical intervention, an unscheduled contact (visit or telephone call) with a physician, temporary cessation of study treatment, or associated with discomfort for the subject such as pain, or impairment of activities of daily life.

Patients with low body weight (≤ 60 kg), CrCL ≤ 50 mL/min, or concomitant use of select P-gp inhibitors were randomized to receive SAVAYSA 30 mg or warfarin. As compared to all patients who received SAVAYSA or warfarin in the 60 mg cohort, all patients who received SAVAYSA or warfarin in the 30 mg cohort (n= 1452, 17.6% of the entire study population) were older (60.1 vs 54.9 years), more frequently female (66.5% vs 37.7%), more frequently of Asian race (46.0% vs 15.6%) and had more co-morbidities (e.g., history of bleeding, hypertension, diabetes, cardiovascular disease, cancer). Clinically relevant bleeding events occurred in 58/733 (7.9%) of the SAVAYSA patients receiving 30 mg once daily and 92/719 (12.8%) of warfarin patients meeting the above criteria.

In the Hokusai VTE study, among all patients the most common bleeding adverse reactions (≥ 1%) are shown in Table 6.4.

Table 6.4: Adverse Reactions Occurring in ≥ 1% of Patients Treated in Hokusai VTE

	SAVAYSA 60 mg (N=4118) n (%)	Warfarin (N=4122) n (%)
Bleeding ADRs[a]		
Vaginal[b]	158 (9.0)	126 (7.1)
Cutaneous soft tissue	245 (5.9)	414 (10.0)
Epistaxis	195 (4.7)	237 (5.7)
Gastrointestinal bleeding	171 (4.2)	150 (3.6)
Lower gastrointestinal	141 (3.4)	126 (3.1)
Oral/pharyngeal	138 (3.4)	162 (3.9)
Macroscopic hematuria/urethral	91 (2.2)	117 (2.8)
Puncture site	56 (1.4)	99 (2.4)
Non-Bleeding ADRs		
Rash	147 (3.6)	151 (3.7)
Abnormal liver function tests	322 (7.8)	322 (7.8)
Anemia	72 (1.7)	55 (1.3)

[a] Adjudicated Any Bleeding by location for all bleeding event categories (including Major and CRNM)

[b] Gender specific vaginal bleeding percentage is based on number of female subjects in each treatment group

7 DRUG INTERACTIONS

7.1 Anticoagulants, Antiplatelets, and Thrombolytics

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs *[see Warnings and Precautions (5.3)]*.

Long-term concomitant treatment with SAVAYSA and other anticoagulants is not recommended because of increased risk of bleeding *[see Warnings and Precautions (5.3)]*. Short term co-administration may be needed for patients transitioning to or from SAVAYSA *[see Dosage and Administration (2.4) in the full prescribing information]*.

In clinical studies with SAVAYSA concomitant use of aspirin (low dose ≤ 100 mg/day) or thienopyridines, and NSAIDs was permitted and resulted in increased rates of Clinically Relevant Bleeding. Carefully monitor for bleeding in patients who require chronic treatment with low dose aspirin and/or NSAIDs *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3) in the full prescribing information]*.

7.2 P-gp Inducers

Avoid the concomitant use of SAVAYSA with rifampin *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

7.3 P-gp Inhibitors

Treatment of NVAF

Based on clinical experience from the ENGAGE AF-TIMI 48 study, dose reduction in patients concomitantly receiving P-gp inhibitors resulted in edoxaban blood levels that were lower than in patients who were given the full dose. Consequently, no dose reduction is recommended for concomitant P-gp inhibitor use *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1) in the full prescribing information]*.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism
[see Clinical Studies (14.2) in the full prescribing information]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies in pregnant women. SAVAYSA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

In the Hokusai VTE study there were 10 pregnancy cases reported in patients receiving SAVAYSA with exposure in the first trimester and estimated duration of exposure for up to approximately 6 weeks. Among these there were 6 live births (4 full term, 2 pre-term), 1 first-trimester spontaneous abortion, and 3 cases of elective termination of pregnancy.

Animal Data

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no teratogenic effects were seen when edoxaban was administered orally at doses up to 300 mg/kg/day, or 49 times the human dose of 60 mg/day normalized to body surface area. Increased post-implantation loss occurred at 300 mg/kg/day, but this effect may be secondary to the maternal vaginal hemorrhage seen at this dose. In rabbits, no teratogenic effects were seen at doses up to 600 mg/kg/day (49 times the human exposure at a dose of 60 mg/day when based on AUC). Embryo-fetal toxicities occurred at maternally toxic doses, and included absent or small fetal gallbladder at 600 mg/kg/day, and increased post-implantation loss, increased spontaneous abortion, and decreased live fetuses and fetal weight at doses equal to or greater than 200 mg/kg/day, which is equal to or greater than 20 times the human exposure.

In a rat pre- and post-natal developmental study, edoxaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 30 mg/kg/day, which is up to 3 times the human exposure when based on AUC. Vaginal bleeding in pregnant rats and delayed avoidance response (a learning test) in female offspring were seen at 30 mg/kg/day.

8.2 Labor and Delivery

Safety and effectiveness of SAVAYSA during labor and delivery have not been studied in clinical studies. The risks of bleeding should be balanced with the risk of thrombotic events when considering the use of SAVAYSA in this setting.

8.3 Nursing Mothers

It is not known if edoxaban is excreted in human milk. Edoxaban was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from SAVAYSA, a decision should be made to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total patients in the ENGAGE AF-TIMI 48 study, 5182 (74%) were 65 years and older, while 2838 (41%) were 75 years and older. In Hokusai VTE, 1334 (32%) patients were 65 years and older, while 560 (14%) patients were 75 years and older. In clinical trials the efficacy and safety of SAVAYSA in elderly (65 years or older) and younger patients were similar *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14) in the full prescribing information]*.

8.6 Renal Impairment

Renal clearance accounts for approximately 50% of the total clearance of edoxaban. Consequently, edoxaban blood levels are increased in patients with poor renal function compared to those with higher renal function. Reduce SAVAYSA dose to 30 mg once daily in patients with CrCL 15-50 mL/min. There are limited clinical data with SAVAYSA in patients with CrCL < 15 mL/min; SAVAYSA is therefore not recommended in these patients. Hemodialysis does not significantly contribute to SAVAYSA clearance *[see Dosage and Administration (2.1, 2.2) and Clinical Pharmacology (12.3) in the full prescribing information]*.

As renal function improves and edoxaban blood levels decrease, the risk for ischemic stroke increases in patients with NVAF *[see Indications and Usage (1.1), Dosage and Administration (2.1), and Clinical Studies (14.1) in the full prescribing information]*.

8.7 Hepatic Impairment

The use of SAVAYSA in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment (Child-Pugh A) *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.8 Low Body Weight Consideration for Patients treated for DVT and/or PE

Based on the clinical experience from the Hokusai VTE study, reduce SAVAYSA dose to 30 mg in patients with body weight less than or equal to 60 kg *[see Dosage and Administration (2.2) and Clinical Studies (14.2) in the full prescribing information]*.

10 OVERDOSAGE

A specific reversal agent for edoxaban is not available. Overdose of SAVAYSA increases the risk of bleeding.

The following are not expected to reverse the anticoagulant effects of edoxaban: protamine sulfate, vitamin K, and tranexamic acid.

Hemodialysis does not significantly contribute to edoxaban clearance *[see Pharmacokinetics (12.3) in the full prescribing information]*.

17 PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

- they may bleed more easily, may bleed longer, or bruise more easily when treated with SAVAYSA
- to report any unusual bleeding immediately to their healthcare provider
- to take SAVAYSA exactly as prescribed
- to not discontinue SAVAYSA without talking to the healthcare provider who prescribed it
- to inform their healthcare providers that they are taking SAVAYSA before any surgery, medical, or dental procedure is scheduled
- to inform their healthcare providers and dentists if they plan to take, or are taking any prescription medications, over-the-counter drugs or herbal products
- to inform their healthcare provider immediately if they become pregnant or intend to become pregnant or are breastfeeding or intend to breastfeed during treatment with SAVAYSA
- that if a dose is missed, take SAVAYSA as soon as possible the same day, and resume the normal dosing schedule the following day. The dose should not be doubled to make up for a missing dose
- that if they are having neuraxial anesthesia or spinal puncture, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Manufactured by:
Daiichi Sankyo Co., LTD.
Tokyo 103-8426
Japan

Distributed by:
Daiichi Sankyo, Inc.
Parsippany, NJ 07054 USA

P1805213-BRIEF/DSSV15000323

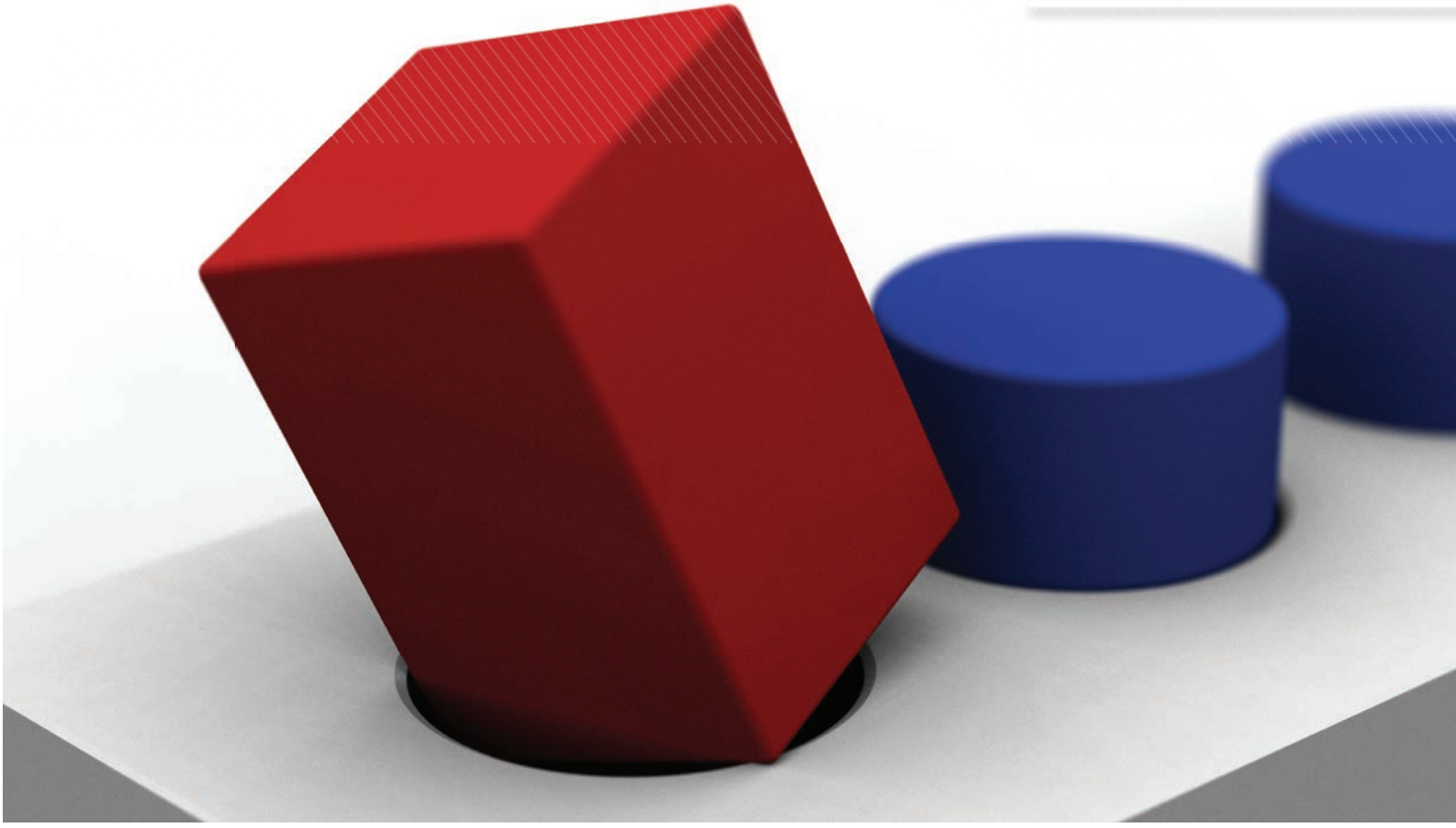
Navigating the challenges of HIV requires innovation

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.

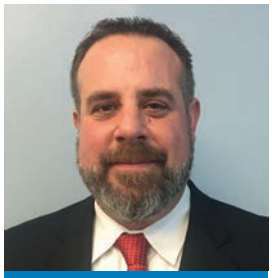
Connect with us at
www.viivhealthcare.com



ViiV Healthcare

PCSK9 Inhibitors and Strategies for Management of Hypercholesterolemia

Lou Zollo, RPh, Senior Director Pharmacy Services, EmblemHealth



Lou Zollo
RPh

Management of hypercholesterolemia, or elevated low-density lipoprotein (LDL-C), is a public health priority. The Centers for Disease Control and Prevention (CDC) reports more than 73 million Americans have high LDL-C. Less than half of these individuals are receiving treatment, and only 29.5 percent have the condition under control.[1] The implications of this data are profound, since individuals with elevated LDL-C have approximately two times greater risk of heart disease, which was attributed to nearly 600,000 deaths in the United States in 2012.[1,2]

Hypercholesterolemia is increasingly recognized as a precipitating factor in the development of atherosclerosis.[3] Meanwhile, reduction in LDL-C levels has been strongly associated with a lower incidence of coronary events and is the objective of managing patients with atherosclerotic cardiovascular disease (ASCVD).[4] Lifestyle modification strategies such as diet, weight control, exercise, and smoking cessation are essential and most often are combined with medications in an effort to combat the effects of high LDL-C and to reduce the risk of ASCVD. HMG-CoA reductase inhibitors (statins) are endorsed within national treatment guidelines as first-line drug therapy for patients with elevated LDL-C, based on years of experience and clinical trial evidence.[5] The 2015 introduction of a new category of biologic agents, proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, offers new options for management of hypercholesterolemia. However, these products may introduce new challenges for payor organizations in terms of cost management. PCSK9 inhibitors have reignited the need for the development and implementation of appropriate policies to manage hypercholesterolemia in a clinically and fiscally responsible manner — optimizing the management and utilization of new and existing therapies to drive superior clinical outcomes.

Current Treatment Guidelines

The availability of the PCSK9 inhibitors coincides with the implementation of the 2013 revisions to guidelines for managing hypercholesterolemia by the American College of Cardiology (ACC) and American Heart Association (AHA), titled "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults."[5] Among the most noteworthy revisions to the guidelines was the elimination of the former LDL-C numeric treatment goals (100 mg/dL or 70 mg/dL, depending on risk factors) as the objective in treatment of hypercholesterolemia. Rather, the new ACC/AHA guidelines focus on reducing cardiovascular risk by lowering LDL-C by specific percentages from baseline. They target a reduction in LDL-C of 50 percent in high-risk patients through the use of high-intensity statin therapy, and a reduction of 30 to 50 percent in patients ≥ 75 years old, or those who are not candidates for high-intensity statins, with moderate-intensity statins.[5] Standardized LDL-C goals were eliminated based on the rationale that they may result in undertreatment.[5] Through the evaluation of numerous clinical studies, the panel concluded that when appropriately utilized, high-intensity statins reduce ASCVD events.[5]

The revised guidelines will likely be used along with the revised 2014 National Lipid Association (NLA) guidelines, which retained the numeric LDL-C treatment goals. The NLA guidelines may be of value in certain practice settings when baseline LDL-C levels are unavailable.[6] Neither guideline is inclusive of PCSK9 inhibitors, which were not available at the time of guideline development.[5]

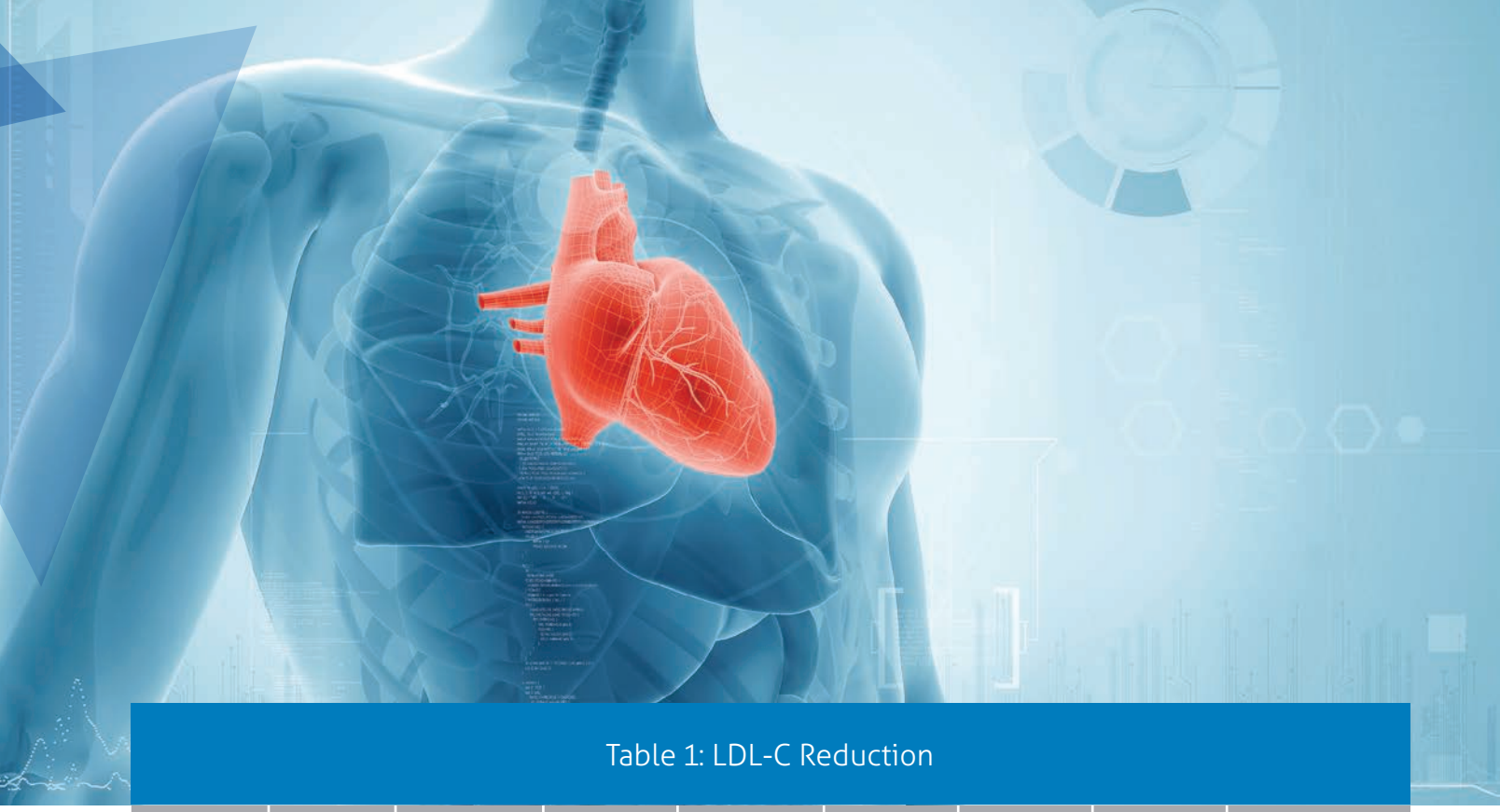


Table 1: LDL-C Reduction

% LDL Reduction	Lovastatin (Mevcor®)	Pravastatin (Pravachol®)	Simvastatin (Zocor®)	Simvastatin/ Ezetimibe (Vytorin®)	Atorvastatin (Lipitor®)	Rosuvastatin (Crestor®)	Alirocumab (Praluent®)	Evolocumab (Repatha™)
25–32%	20 mg	20 mg	10 mg	-	-	-	-	-
31–39%	40 mg	40 mg	20 mg	-	10 mg	-	-	-
37–45%	80 mg	80 mg	20 mg	10/10	20 mg*	5 mg	-	-
48–52%	-	-	80 mg	10/20	40 mg*	10 mg	-	-
55–60%	-	-	-	10/40	80 mg*	20 mg*	75 mg*	-
60–63%	-	-	-	10/80	-	40 mg*	150 mg*	140 mg every 2 weeks or 420 mg once monthly

**High-intensity therapy Information derived from respective product package insert.*

The ACC/AHA guideline revisions have already demonstrated a profound influence over national quality rating systems. For example, the 2015 American Diabetic Association Guidelines for Management of Cholesterol in Diabetics were updated, and Healthcare Effectiveness Data and Information Set (HEDIS) measures were revised (statin-therapy measures were added in 2016, replacing the former HEDIS LDL-C based measures from 2015).[7-10] Ultimately the guideline revisions will influence the therapeutic management of hypercholesterolemia, including the role in therapy and management of the PCSK9 inhibitors.

Payor coverage criteria may take into consideration both the ACC/AHA and the NLA guidelines, in order to optimize clinical outcomes in all patient types, must be clinically relevant, and may include LDL-C goals as appropriate.

Familial Hypercholesterolemia

Among patients with hypercholesterolemia, some may have a genetic predisposition to elevated levels of LDL-C, known as familial hypercholesterolemia (FH), placing them at higher risk of ASCVD. Customarily, FH is classified as either homozygous (HoFH) or heterozygous (HeFH). The HeFH variant is most common, occurring in approximately one in 300 to 500 individuals worldwide.[11] The homozygous form of hypercholesterolemia (HoFH), while typically more difficult to treat, is estimated to have a much lower incidence, occurring in approximately one of every 1 million individuals.[11] With the high prevalence of FH and associated morbidity and mortality, aggressive screening and treatment is warranted. There are

two major challenges to FH treatment: the failure to identify patients who have increased risk, and the inability of patients on many therapies to achieve goals.[12] New genetic screening techniques, along with the addition of potent statin therapy, have helped to address these issues.[13] The introduction of PCSK9 inhibitors adds yet another tool to the armamentarium of FH treatment options.

Statin Clinical Management Strategies

While statins are generally well-tolerated, patient-specific drug selection and monitoring remain crucial. For example, consideration of chronic conditions such as diabetes is key to avoiding potential adverse effects.[13] Additionally, monitoring for known side effects associated with statin therapy is important.[14]

Of particular priority is the clear definition and management of statin intolerance, a condition often associated with statins, but for which definitive diagnostic criteria are lacking. As a result, it is believed that statin intolerance is likely to be overdiagnosed. With the availability of the PCSK9 inhibitors, criteria for the accurate diagnosis of statin intolerance take on renewed significance. The PCSK9 inhibitors are approved as an adjunct to diet and maximally tolerated statins in patients not meeting LDL-C goals.[15,16] In the absence of an adequate trial with statins, patients may miss an opportunity to manage hypercholesterolemia with statins alone, and treatment with PCSK9 inhibitors may begin prematurely or occur at a higher frequency than warranted.

Consideration must be given to the actual incidence of statin intolerance. In trials of PCSK9 inhibitors, investigators reported that up to 20 percent of patients with dyslipidemia are statin intolerant, with most cases of intolerance resulting from muscle-related adverse events.[17] A review of the literature revealed two studies that demonstrated that upon retrial with statins, 72 to 90 percent of patients previously identified as statin intolerant were, in fact, tolerant of statin therapy.[14,18] Specifically, in a Cleveland Clinic study of patients classified as "statin intolerant," 72 percent of patients with prior statin intolerance were able to successfully tolerate a statin during retrials, with 63 percent on a daily regimen and 9 percent on an intermittent statin regimen.[18] Of patients defined as statin intolerant, more than 70 percent had been or were being treated with atorvastatin (Lipitor®).[18]

These studies demonstrate the importance of developing comprehensive high-risk cholesterol management strategies. The evidence suggests that many patients believed to be statin intolerant can actually tolerate some form of statin therapy, and that for patients unable to tolerate daily dosing, there is value in intermittent statin dosing to aid in achievement of LDL-C lowering goals. Prior to determining if a patient is statin intolerant, it is critical to first rule out other factors that may be contributing to adverse events potentially related to statins. Additional strategies for managing intolerance may include: switching therapy to an alternative statin, alternate day dosing, or treatment with nonstatin therapies.[14]

PCSK9 Therapy

Regarding PCSK9 inhibitors and their mechanism of action, while the statins interfere with cholesterol synthesis, the PCSK9 inhibitors work through an entirely different mechanism of action, making them an appropriate adjunct in therapy

Table 2: Product Comparison[16,19,26]

	Alirocumab (Praluent®)	Evolocumab (Repatha™)
Manufacturer	Regeneron/Sanofi	Amgen
Approval Date	July 24, 2015	August 27, 2015
Dosing Frequency	75 mg to 150 mg every 2 weeks	140 mg every 2 weeks or 420 mg once monthly
Studied Populations		
• Hereditary familial hypercholesterolemia (heterozygous)	√	√
• Hereditary familial hypercholesterolemia (homozygous)	Not studied	√
• Statin intolerance	√	√
• Primary treatment as monotherapy (without statins)	√	√
• Patients with LDL-C above treatment goal despite maximal statin therapy	√	√
• Cardiovascular high-risk patients	√	√
• Efficacy (LDL lowering vs. placebo)	Approximately 40–60%	Approximately 40–70%
WAC* Pricing per Dose	$1,120.00**	$1,084.62**
WAC* Annual Cost	$13,440.00**	$13,015.44**

**Wholesale Acquisition Cost **Source: Truven Health Analytics*

for certain patients. PCSK9 inhibitors consist of secreted 692-amino acid protein that binds surface LDL receptors (LDLRs) and targets them for lysosomal degradation. As a consequence, the number of LDLRs at the cell surface is decreased, and LDL-C clearance is reduced, a phenomenon that is magnified by gain-of-function mutations of PCSK9 inhibitors. In contrast, loss-of-function mutations of PCSK9 inhibitors result in increased surface LDLRs and improved LDL-C clearance. This provides the rationale for targeting PCSK9 inhibitors in hypercholesterolemic subjects as a means of lowering LDL-C levels.[15]

Monoclonal antibodies (mAbs) against the PCSK9 protein that block its interaction with the LDLR have been developed, including evolocumab (Amgen's Repatha™) and alirocumab (Sanofi and Regeneron Pharmaceuticals' Praluent®).[16,19] Table 2 discusses the PCSK9 inhibitors in further detail. Both agents were approved for primary hyperlipidemia as an adjunct to diet and maximally tolerated statin therapy in the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL.[16,19] Evolocumab also received approval for homozygous familial hypercholesterolemia.[19] A meta-analysis of published studies demonstrating the safety and efficacy of PCSK9 inhibitors indicated they are associated with lower odds of all-cause mortality and myocardial infarction (MI); a nonsignificant reduction in cardiovascular mortality; a reduction in atherogenic lipids; a lower increase in serum creatine kinase levels; and no increase in serious adverse events. The magnitude of reduction of LDL-C was greater with PCSK9 inhibitors than with ezetimibe (Zetia®), and reduction in lipoprotein(a) may contribute to the reduction in mortality and MI rates, which may suggest another possible long-term cardiovascular benefit of PCSK9 inhibitors. The researchers concluded the data available suggests these agents are safe and effective.[20]

While recognizing the clinical attributes of the PCSK9 inhibitors, the health care system faces a formidable economic challenge in managing the uptake of these agents. Hypercholesterolemia is a high incidence condition, with profound clinical implications, which make it a clinical management priority. Statins, the majority of which are available generically, offer a low-cost and effective management strategy. The financial impact of widespread utilization of the PCSK9 inhibitors, priced in the neighborhood of $14,000 per year per patient, is a concern. Without effective management, payors may be confronted with a budget buster rivaling the impact of hepatitis C therapies in recent years. The cost per course of treatment is not as high, but the incidence and potential demand for these agents could, without effective management, have staggering financial implications.

Payor Policies

In an effort to optimize clinical outcomes and provide appropriate access to cholesterol-lowering therapies, including PCSK9 inhibitors, payor policies for high-risk cholesterol management may include documented requirements for trial and failure with specific agents and/or dosages prior to allowing access to PCSK9 inhibitors. Additionally, payors may decide to identify a number of other requirements designed to optimize the use and efficacy of high-intensity statin therapies, including a requirement for the demonstration of adherence with statin therapy, as well as statin intolerance criteria, such as:

- Dose titration
- Rechallenge with high-intensity statins
- Trial with alternative products
- Intermittent dosing trial

When refining medical policies for hypercholesterolemia management, it is important to highlight potential advantages offered by individual products, especially if these products can be utilized to enhance cost-effective outcomes. For example, rosuvastatin (Crestor®), a synthetic statin, decreased LDL-C by 58 percent while increasing high-density lipoprotein (HDL-C) levels by 12 percent in HeFH patients, and has been shown to be significantly superior to high-dose atorvastatin in improving these lipid parameters, as well as total cholesterol, apolipoprotein (apo) B, apo A-I, and the LDL-C/HDL-C ratio.[12]

Criteria inclusive of a required trial with rosuvastatin (anticipated to be available as a generic formulation in 2016) might be evaluated. Payor policies may take into consideration the MERCURY II Trial, which demonstrated more patients achieved their LDL-C target when switched to rosuvastatin from atorvastatin or simvastatin;[21] the ECLIPSE Study, which demonstrated LDL-C reductions across the rosuvastatin dose range, with more high-risk patients achieving LDL-C goal than with atorvastatin and a reported decrease in LDL-C of 47 to 57 percent;[22] and the RADAR study, which demonstrated a change in LDL-C of 44 to 55 percent in rosuvastatin-treated patients, compared with 38 to 48 percent for patients treated with atorvastatin.[23]

Finally, in the development of a high-risk cholesterol management strategy, payor policies may consider the favorable findings reported in the IMPROVE-IT study.[24] This study demonstrated the benefits of the addition of ezetimibe to a statin regimen in reducing the incidence of cardiovascular death, a composite measure by 6.4 percent when administered with simvastatin, compared with patients who received simvastatin alone.[24]

Payors may consider development of clinical management criteria for hypercholesterolemia in high-risk patients that may include a requirement that therapy begin with a maximum tolerated dose of statins in high-risk patients, and that, when appropriate, and LDL-C reduction targets are not reached, addition of other agents such as ezetimibe be considered.[25] Ezetimibe, co-administered with rosuvastatin or another payor-identified clinically appropriate high-intensity statin regimen, along with a demonstration of adherence with therapy, may serve as a foundation for a policy that allows access and coverage for PCSK9 inhibitors.

Conclusion

High-risk cholesterol management programs must be thoughtfully developed and proactive — balancing the clinical with the economic aspects of the management of hypercholesterolemia.

They must be designed with the objective of optimizing outcomes by maximizing the clinical benefits of statins. Policies must leverage the value PCSK9 inhibitors offer as an additional treatment option for patients with severe hypercholesterolemia who are unable to attain LDL-C goals, despite documented trial and failure of maximally tolerated high-intensity statin therapy. While focusing on optimizing clinical outcomes and supporting payor priorities related to quality measures, policies should integrate treatment guidelines. They should include clear criteria for demonstrating adherence with maximally tolerated statin therapy and for defining statin intolerance — including requirements for a rechallenge with high-intensity statin therapy and, potentially, a documented trial of alternative options. Collectively these efforts will support the initiation of therapy with PCSK9 inhibitors in a manner consistent with FDA-approved labeling. As a result, patients treated with PCSK9 inhibitors will be adherent to high-intensity statin therapy, have implemented lifestyle modifications, and when appropriate, utilize other nonstatin therapies such as ezetimibe.

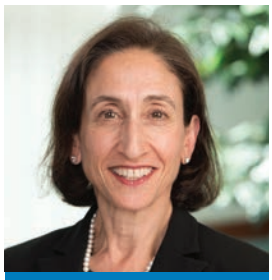
In developing policies, plans may include a step-therapy requirement for a documented trial and failure of multiple cholesterol-lowering agents prior to the approval/coverage of a PCSK9 inhibitor to help minimize risk of overutilization. Since the majority of patients are likely to have had a trial with atorvastatin, a requirement for a trial of only one high-intensity statin may permit access to PCSK9 inhibitors for a majority of patients. Specifically, payors may benefit from including a specific requirement for a trial of rosuvastatin and ezetimibe. This approach may yield maximum LDL-C reduction, leveraging the additive effect of ezetimibe with the potency of rosuvastatin, in anticipation of its generic availability in the coming year. A well-structured plan for PCSK9 management will enable plans to provide access to the PCSK9 inhibitors when clinically warranted while managing the clinical and financial implications of overseeing hypercholesterolemia and specific therapies such as the PCSK9 inhibitors.

REFERENCES

1. High cholesterol facts. Centers for Disease Control and Prevention website. **www.cdc.gov/cholesterol/facts.htm.** Accessed January 12, 2016.
2. Heron M. Deaths: Leading causes for 2012. National Vital Statistics Reports. 2015;64(10):9. **www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_10.pdf.** Accessed January 28, 2016.
3. Li S, Li J. PCSK9: A key factor modulating atherosclerosis. *J Atheroscler Throm.* 2015;22:221-230.
4. Goldstein JI, Brown MS. A century of cholesterol and coronaries: From plaques to genes to statins. *Cell.* 2015;161(1):161-172.
5. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation.* November 12, 2013. **http://circ.ahajournals.org/content/129/25_suppl_2/S1.** Accessed January 28, 2016.
6. Jacobson T, Ito M, Maki K, et al., National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. *J Clin Lipidol.* 2014;8:473-488. **www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf.** Accessed January 12, 2016.
7. National Committee for Quality Assurance. Proposed retirement for HEDIS 2015: Cholesterol management for patients with cardiovascular conditions (CMC). **www.ncqa.org/Portals/0/HomePage/CMC.pdf.** Accessed January 5, 2016.
8. NCQA updates HEDIS quality measures for 2016. National Committee for Quality Assurance. News release. July 1, 2015. **www.ncqa.org/Newsroom/NewsArchive/2015NewsArchive/NewsReleaseJuly12015.aspx.** Accessed January 11, 2016.
9. National Committee for Quality Assurance. Summary table of measures, product lines and changes. **www.ncqa.org/Portals/0/HEDISQM/Hedis2015/List_of_HEDIS_2015_Measures.pdf.** Accessed January 11, 2016.
10. Standards of medical care in diabetes — 2015: Summary of revisions. *Diabetes Care.* 2015;38(1 S4). **http://care.diabetesjournals.org/content/38/Supplement_1/S4.full.** Accessed January 28, 2016.
11. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J.* 2014. **http://eurheartj.oxfordjournals.org/content/early/2014/07/22/eurheartj.ehu274.** Accessed January 28, 2016.
12. Ballantyne CM. Familial hypercholesterolemia: Optimum treatment strategies. *Int J Clin Pract Suppl.* 2002;(130):22-26.
13. Robinson J. Management of familial hypercholesterolemia: A review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Manag Care Pharm.* 2013;19(2):139-149.
14. Raju S, Varghese K. Management of statin intolerance. *Indian J Endocrinol Metab.* 2013;17(6):977–982.
15. Shimada YJ, Cannon CP. PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: Past, present, and the future. *Eur Heart J.* 2015;36(36):2415-2424.
16. Alirocumab (Praluent®) [package insert]. Regeneron Pharmaceuticals, Inc./Sanofi-Aventis U.S. LLC; July 2015.
17. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: The GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol.* 2014;63(23):2541-2548.
18. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: The Cleveland Clinic experience. *Am Heart J.* 2013;166:597-603.
19. Evolocumab (Repatha™) [package insert]. Amgen Inc.; September 2015.
20. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: A systematic review and meta-analysis. *Ann Intern Med.* 2015;163(1):40-51.
21. Ballantyne CM, Bertolami M, Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY) II. *Am Heart J.* 2006;151(5):975.e1-975.e9.
22. Faergeman O, Hill L, Windler E, et al. Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia. *Cardiology.* 2008;111:219-228.
23. Jukema JW, Liem A-H, Dunselman PHJM, et al. LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: Results of the RADAR (rosuvastatin and atorvastatin in different dosages and reverse cholesterol transport) study. *Curr Med Res Opin.* 2005;21(11):1865-1874.
24. Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation.* 2015;132(13):1224-1233.
25. Hartgers M, Ray K. New approaches in detection and treatment of familial hypercholesterolemia. *Curr Cardiol Rep.* 2015;17(12):109.
26. Micromedex Solutions. **www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/BC07B4/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/E96026/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/redbook.ShowProductSearchResults?SearchTerm=PRALUENT&searchType=redbookProductName&searchTermId=43937&searchContent= REDBOOK&searchFilterAD=filterADActive&searchFilterRepackager=filterExcludeRepackager&searchPattern=%5Epra.** 2016. Accessed January 14, 2016.

Immunotherapies: PD-1 Inhibitors Changing Cancer Treatment

Leslie Fish, PharmD, Vice President Pharmacy Services, Fallon Health



Leslie Fish
PharmD

Immunotherapy, selected by *Science*'s editors as medical breakthrough of the year for 2013,[1] represents a radical shift in the approach in treating advanced solid tumors. Rather than using the traditional chemotherapy-based approach of "poisoning" cancer cells, immunotherapy harnesses the capabilities of the immune system to exploit the behavior of tumor cells and to target cancer cells directly.[1] Today, two monoclonal antibodies (mAbs) for immunotherapy, pembrolizumab (Keytruda®, Merck) and nivolumab (Opdivo®, Bristol-Myers Squibb), are approved in the United States.[2]

Keytruda and Opdivo were first approved to treat melanoma.[3,4] Their list of approved uses has expanded to include treatment of non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC),[3,4] with additional clinical trials underway to study their potential use in numerous tumor types, as seen in Table 1.

An overview of how these agents can be effective must begin with the explanation that some tumors circumvent the immune system by interfering with the normal detection process intended to prevent tumor proliferation. The key elements of this process are the body's immune cells, or T-cells, and two proteins. The first protein, programmed death-1 (PD-1), is found on the surface of the immune cells, and the second protein, programmed death ligand-1 (PD-L1), is expressed on the cancer cells. When PD-L1 from the tumor cell binds with the PD-1 on the immune cell, the combination forms a biochemical shield that protects tumor cells from being destroyed by the immune system.[6] The new immunotherapies, termed PD-1 inhibitors and anti-PD-1s, are also referred to as "checkpoint inhibitors." PD-1 inhibitors exert their therapeutic effect by working at the site of the PD-1 and PD-L1 proteins to disable the biological "off switch" and as a result augmenting the body's ability to mount an immune system response against tumor cells.[7-9]

Analysts are estimating that sales of oncology immunotherapy agents, including PD-1 and anti-PD-L1 products and others in development, could be in the range of $20 to $33 billion by 2022.[10] The excitement surrounding these therapies is profound and, not surprisingly, they are of widespread clinical and financial interest.

A New Approach to Advanced Melanoma

Keytruda was the first anti-PD-1 launched in the United States, earning FDA approval in 2014 as a treatment for unresectable or advanced melanoma, with Opdivo receiving approval soon afterward. Both PD-1 inhibitors are intended for melanoma patients previously treated with ipilimumab (Yervoy®, Bristol-Myers Squibb) and a BRAF inhibitor (if BRAF V600 gene mutation positive).[3,4] The potential role of these agents in melanoma treatment continues to expand as research finds a role for them as part of combination therapy regimens for various forms of disease, including specific disease mutations. For example, in early 2016, the FDA approved Opdivo for use in combination with Yervoy for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma.[11]

As expanded indications arise, the clinical and economic impact of the anti-PD-1 therapies in treating melanoma is evident in light of the fact that nearly 74,000 patients are diagnosed annually with melanoma, and that the disease represents approximately 5 percent of all new cancers in the United States.[12] Survival rates for metastatic melanoma, which encompasses stage IV cancer, are poor; the 10-year survival rate is 15 to 20 percent.[13]

Although data regarding the long-term survival rates for melanoma patients treated with PD-1 inhibitors is still emerging, clinical trials show promise for increased longevity. In phase 3 trials, Keytruda demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) for patients with unresectable stage III or IV advanced melanoma (see Table 2).[14] The data was compelling: Estimated PFS rates for the Keytruda treatment arm were 47.3 percent and 46.4 percent (administered at two- and three-week intervals, respectively), compared with 26.5 percent for Yervoy. The Keytruda response rates of 32.9 to 33.7 percent exceeded those of Yervoy, which were 11.9 percent. Significantly, at a median follow-up of 7.9 months, responses were ongoing in 89.4 percent to 96.7 percent of Keytruda patients.[14] Finally, and of note, 12-month survival rates for patients treated with Keytruda ranged from 68.4 to 74.1 percent.[14]

Opdivo is approved for unresectable or metastatic BRAF V600 mutation-positive melanoma and disease progression following Yervoy and a BRAF inhibitor; it is also approved as monotherapy as well as for administration in combination with Yervoy for treatment of BRAF V600 wild-type unresectable or metastatic melanoma.[3] The CheckMate-069 clinical trial explored use of Opdivo in combination with Yervoy, which exerts its effect as an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody.[15] Among 142 trial participants with previously untreated advanced melanoma, better results in objective response rate (ORR), defined as a measurable response by the National Cancer Institute endpoints,[16] were seen in patients taking the combination therapy than in participants treated with Yervoy monotherapy. The combined regimen achieved an ORR of 61 percent, compared with 11 percent for Yervoy alone.[17]

Expanded Indications Yield More Patient Candidates for PD-1 Inhibitors

The use of PD-1 inhibitors expanded rapidly following their approval for advanced melanoma (see Table 3). As of publication, PD-1 inhibitors were also indicated for:

Advanced lung cancer: Keytruda and Opdivo received approval within a week of each other in 2015 for use in patients with advanced NSCLC.[3,4] These approvals suggest the potential to make a meaningful clinical impact on the treatment of lung cancer — the leading cause of cancer death in the United States, with an estimated 158,000 deaths in 2015.[18] The most common type of lung cancer, NSCLC affects seven out of eight lung cancer patients.[19]

Keytruda is indicated for treatment of NSCLC in patients with PD-L1-expressing tumors experiencing disease progression on or after platinum-containing chemotherapy.[4] The appropriateness of Keytruda as a treatment is assessed by conducting an FDA-approved diagnostic test (PD-L1 IHC 22C3 pharmDx™).[4]

Opdivo is approved for the treatment of metastatic NSCLC in patients whose disease progressed during or after platinum-based chemotherapy. Patients with genomic tumor aberrations, EGFR or ALK, should have disease progression on FDA-approved EGFR- or ALK-directed therapies prior to treatment with Opdivo.[3]

While study results demonstrate an overall survival benefit in treating select NSCLC patients with PD-1 inhibitors, appropriate identification of patients is critical. Therefore, payor coverage criteria for these therapies requires the implementation of policies — including step therapy for medications that must be tried prior to the PD-1 inhibitors — and defined criteria for diagnostic testing. Payors will benefit from the implementation of these strategies as a means of assuring these therapies are managed, while still available for appropriately identified patients with the highest likelihood of favorable clinical outcomes from their use.

Renal cell carcinoma: Opdivo is approved for use in patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. Studies that supported the FDA approval of Opdivo for this condition demonstrated that patients lived an average of 25 months after starting treatment with Opdivo, compared with 19.6 months in those treated with everolimus (Afinitor®, Novartis).[3] This benefit was observed regardless of the PD-L1 expression level in participants' renal cell tumors. Additionally, 21.5 percent of those treated with Opdivo experienced a complete or partial tumor reduction, lasting an average of 23 months, compared with those treated with Afinitor, with a response rate of 3.9 percent for an average duration of 13.7 months. This scenario once again has clinical and financial relevance as renal cell carcinoma is the most common form of adult kidney cancer; an estimated 61,500 new kidney and renal pelvis cancers occur annually.[20]

Implications for Managed Care

The availability of PD-1 inhibitors and other advances in cancer treatment will require payors to reconsider their approach to oncology care coverage. Historically, oncology medication coverage policies centered primarily on providing access to treatment for FDA-approved indications for use of a particular therapy, and patients either met these requirements or did not. These generally included medical necessity criteria based on FDA-approved indications for use of these drugs — in the case of PD-1 inhibitors, the approved labeling for use in either advanced melanoma, NSCLC, or renal cell carcinoma.[21-23] Additionally, coverage criteria typically included requirements for prior treatments or documented treatment failures, detailed

Table 1: Additional Tumor Types/Conditions in Which PD-1s Are Being Studied[5]

Keytruda	Opdivo
Biliary cancer	Bladder cancer
Bladder cancer	Brain metastases
Bone cancer (osteosarcoma)	Breast cancer
Brain metastases	Colorectal cancer
Breast cancer	General blood malignancies
Colorectal cancer	Glioblastoma multiforme
Esophageal cancer	Glioma
Gastrointestinal adenocarcinoma	Head and neck cancers
General blood malignancies	Hepatitis C treatment
Germ cell tumor	Hepatoma, liver cancer
Glioblastoma multiforme	Hodgkin's lymphoma
Glioma	Leukemia, acute myeloid (AML)
Head and neck cancers	Leukemia, chronic lymphocytic (CLL)
Hodgkin's lymphoma	Leukemia, chronic myeloid (CML)
Melanoma	Melanoma
Mesothelioma	Multiple myeloma
Multiple myeloma	Myelodysplastic syndrome
Neuroendocrine tumor	Non-Hodgkin's lymphoma
Non-Hodgkin's lymphoma	Non-small cell lung cancer (NSCLC)
Non-small cell lung cancer (NSCLC)	Pancreatic cancer
Ovarian cancer	Renal cell carcinoma
Pancreatic cancer	Small cell lung cancer
Prostate cancer	Solid tumor indications
Renal cell carcinoma	Stomach cancer
Small cell lung cancer	
Soft tissue sarcoma	
Solid tumor indications	
Stomach cancer	
Uterine cancer	

necessary concomitant therapies, and in some instances contraindications to treatment. For example, increasingly, payor guidance may include therapy-specific requirements, such as the Eastern Cooperative Oncology Group (ECOG) performance status assessment, to ascertain that patients meet a minimum level of wellness prior to being considered candidates for treatment.[22]

Traditionally, clinical treatment guidelines such as those published and updated regularly by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) serve as a general clinical framework for management of oncology treatments and, by default, influence payor coverage policies. Historically, these guidelines have not included a financial assessment of therapies. This is changing as NCCN and ASCO guidelines have started to evolve, driven in part by the availability of higher-cost drugs. NCCN and ASCO are beginning to integrate other considerations such as economics, survival, and quality of life into their resources (NCCN Evidence Blocks and ASCO Value Framework).[24,25]

It is recognized that the clinical trials supporting the FDA approval of Opdivo and Keytruda demonstrate that these agents may provide quicker and potentially more effective treatment than previously available, complex, and longer-duration treatment regimens. Compared with chemotherapy, PD-1 inhibitors may improve survival rates and enhance quality of life — in part due to a lower level of toxicity associated with therapy in correctly identified and clinically responsive patients.

Payors must keep PD-1 inhibitors in their sights as science deliberates the identification and role of biomarkers to predict the effectiveness of PD-1 inhibitors, as this may result in valuable tools that support the appropriate selection of patients and personalization of oncology regimens. This is a work in progress. While PD-L1 expression may be useful in determining the effectiveness of anti-PD-1 therapies, assays are difficult to develop and interpret. Research continues regarding the role of PD-L2 and its contribution to some tumors, as well as the potential efficacy of combinations of PD-1 inhibitors, or anti-PD-L1 agents with other drugs. Each of these pieces of information will provide insight that may impact outcomes and influence payor coverage strategies. One thing is certain: The management of PD-1 agents by payors demands the attention of both clinicians and payors. As a better understanding of how the tumor microenvironment and immune system interact and the identification of markers that can predict outcomes emerge, these insights will inform decisions regarding which patients will benefit most from these agents and shape coverage policies.[26,27]

It is critical to note that, in addition to being clinically relevant, determining which patients are most likely to have a positive response to PD-1 inhibitors is a crucial financial issue. Payors, along with Medicare, are required to cover cancer therapies that follow FDA indications for use, and they will benefit from this insight given the high costs of these therapies.[28] Single-drug treatments can cost $150,000 annually, while combination therapies involving a PD-1 inhibitor can reach $300,000.[28] These costs will be considered within the new oncology guidelines being developed, such as the NCCN Evidence Blocks and ASCO Value Framework. All this being said, payors are currently managing access to the therapies largely by requiring that patients meet FDA indications and/or treatment guidelines largely based upon approved indications.

Future Directions

As the oncology community engages in discussion about biomarkers and drug costs, research to expand the use of PD-1 inhibitors continues at a rapid pace. Bristol-Myers Squibb and Merck are studying the effectiveness of Keytruda and Opdivo as either monotherapies or in combination with other therapies for treatment of multiple tumor types in more than 135 trials involving over 22,000 patients.[29,30] Other PD-1 inhibitors are also being investigated, including AstraZeneca's anti-PD-L1 antibody durvalumab (MEDI4736), for the treatment of advanced NSCLC, and Roche's atezolizumab (MPDL3280A, anti-PDL1), for advanced NSCLC and bladder cancer.[31,32] PD-1 inhibitors are also being studied as treatments for other malignancies, as seen in Table 1, including metastatic Hodgkin's lymphoma, non-Hodgkin's lymphoma, ovarian cancer, urothelial cancer, colon cancer, metastatic triple-negative breast cancer, and other solid tumors. The results of trials show promise — a 2015 trial showed Opdivo significantly shrank tumors in 19 percent of liver cancer patients,[33] while Keytruda reduced tumor size in 24.8 percent of head and neck cancer patients.[34]

As PD-1 inhibitors receive approval for expanded use or are used as first-line therapies, the health care system will be tasked with integrating these agents into the treatment paradigm along with other cancer drugs. Consideration must be given to the impact of these agents on overall outcomes, including duration of treatment, quality of life, morbidity, and mortality. PD-1 inhibitors could conceivably contribute to some cancers becoming chronic ailments, similar to type 2 diabetes or hypertension, that require ongoing and long-term pharmaceutical treatment.[28] It will be incumbent upon payors and the health care system in its entirety to manage the clinical and financial implications of PD-1 inhibitors as they emerge as frontline therapies for currently approved indications, and as potential treatments for the multiple tumor types for which they might be approved in the future.

Table 2: Key Clinical Trials[14,17,35-40]

Key Studies	Number of Patients and Study Duration	Dosing	Primary Endpoints/Results
KEYTRUDA			
KEYNOTE-001 Phase I Study of Single Agent Keytruda in Patients With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma	Open-label, multicenter cohort phase 1 trial consisting of 173 patients, ages 18 to 88, with unresectable or metastatic melanoma with disease progression within 24 weeks of last dose of Keytruda, and if BRAF V600 mutation positive, received prior treatment with a BRAF inhibitor. Median follow-up duration was eight months.	Patients were given intravenous Keytruda at 2 mg/kg every three weeks (n=89) or 10 mg/kg (n=84) every three weeks until disease progression, intolerable toxicity, or consent withdrawal.	Overall response rate (ORR) was 26% at both doses: 21 of 81 patients in the 2 mg/kg group and 20 of 76 in the 10 mg/kg group. Findings suggest that Keytruda at a dose of 2 mg/kg or 10 mg/kg every three weeks could be an effective treatment option for patients with Yervoy-refractory advanced melanoma, a population for whom there are few effective treatment options. The FDA-expanded indication for use of Keytruda in individuals with metastatic NSCLC whose tumors express PD-L1 and have disease progression on or after platinum-containing chemotherapy is based on findings from the Phase 1 KEYNOTE-001 trial.
KEYNOTE-006 A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Keytruda Compared to Yervoy in Patients With Advanced Melanoma	834 patients with advanced melanoma	Patients were selected to receive Keytruda (at a dose of 10 mg/kg) every two weeks or every three weeks or four doses of Yervoy (3 mg/kg) every three weeks.	Primary endpoints were progression-free survival (PFS) and overall survival (OS): The estimated six-month PFS rates were 47.3% for Keytruda every two weeks, 46.4% for Keytruda every three weeks, and 26.5% for Yervoy. Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively. The response rate was improved with Keytruda administered every two weeks (33.7%) and every three weeks (32.9%), as compared with Yervoy (11.9%). Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively, after a median follow-up of 7.9 months. Efficacy was similar in the two Keytruda groups. Rates of treatment-related adverse events of grade 3 to 5 severity were lower in the Keytruda groups (13.3% and 10.1%) than in the Yervoy group (19.9%).
OPDIVO			
CHECKMATE-037 TRIAL A Randomized Open-Label Phase 3 Trial of Opdivo Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy	The FDA-accelerated approval of Opdivo was based on preliminary data from the CheckMate-037 trial. Continued approval of Opdivo is contingent on confirmatory trials underway. The single-arm, open-label, multicenter phase 3 trial randomized subjects 2:1 to Opdivo or chemotherapy (physician's option of dacarbazine or carboplatin and paclitaxel). All subjects had disease progression following Yervoy and a BRAF inhibitor, if the V600 mutation was positive. The preliminary data reported 120 subjects (median age 59.5 years) with unresectable or metastatic melanoma with disease progression within 24 weeks of their last dose of Yervoy, and if BRAF V600 mutation positive, prior treatment with BRAF inhibitor.	Opdivo or chemotherapy (physician's option of dacarbazine or carboplatin and paclitaxel)	ORR was achieved in 32% of Opdivo subjects. Of the 38 subjects with responses, 33 had duration from 2.6 to 10 months (13 subjects had response of six months or more).

continued on page 28

PD-1 Inhibitors *continued*

Table 2: continued from page 27

CHECKMATE-066 TRIAL A Phase 3, Randomized, Double-Blind Study of Opdivo vs. Dacarbazine in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma	418 previously untreated patients who had metastatic melanoma without a BRAF mutation to receive Opdivo or dacarbazine	Patients received Opdivo (at a dose of 3 mg/kg every two weeks and dacarbazine-matched placebo every three weeks) or dacarbazine (at a dose of 1,000 mg per square meter of body-surface area every three weeks and Opdivo-matched placebo every two weeks).	At one year, the overall rate of survival was 72.9% in the Opdivo group, as compared with 42.1% in the dacarbazine group. The median PFS was 5.1 months in the Opdivo group vs. 2.2 months in the dacarbazine group. The objective response rate was 40% in the Opdivo group vs. 13.9% in the dacarbazine group.
CHECKMATE-067 TRIAL A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab Versus Ipilimumab Monotherapy in Subjects With Previously Untreated Unresectable or Metastatic Melanoma	945 treatment-naïve participants with histologically confirmed stage III (unresectable) or IV metastatic melanoma to receive Opdivo alone (n=316), Opdivo plus Yervoy (n=314), or Yervoy alone (n=315)	In this double-blind, phase 3 study, enrolled patients were randomly assigned in a 1:1:1 ratio to receive one of the following regimens: 3 mg/kg of Opdivo every two weeks (plus Yervoy-matched placebo); 1 mg/kg of Opdivo every three weeks plus 3 mg/kg of Yervoy every three weeks for four doses, followed by 3 mg/kg of Opdivo every two weeks for cycle three and beyond; or 3 mg/kg of Yervoy every three weeks for four doses (plus Opdivo-matched placebo). Both Opdivo and Yervoy were administered by means of intravenous infusion.	The median PFS was 11.5 months with Opdivo plus Yervoy, as compared with 2.9 months with Yervoy and 6.9 months with Opdivo. In patients with tumors positive for the PD-1 ligand (PD-L1), the median PFS was 14 months in the Opdivo-plus-Yervoy group and in the Opdivo group, but in patients with PD-L1-negative tumors, PFS was longer with the combination therapy than with Opdivo alone (11.2 months vs. 5.3 months). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the Opdivo group, 55% of those in the Opdivo-plus-Yervoy group, and 27.3% of those in the Yervoy group.
CHECKMATE-069 TRIAL Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination With Ipilimumab vs. Ipilimumab Alone in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma (The FDA-expanded indication for combination use of Opdivo and Yervoy as treatment of individuals with BRAF V600 wild-type unresectable or metastatic melanoma is based on findings from the phase 2 CheckMate-069 study.)	Double-blind trial with 142 treatment-naïve participants with stage III/IV melanoma	Randomized in a 2:1 ratio to receive Yervoy plus Opdivo (n=95) or Yervoy monotherapy (n=47) until disease progression or death	The rate of confirmed objective response among participants with BRAF V600 wild-type tumors was 61% (44 of 72 participants) in the group that received combination therapy vs. 11% (4 of 37 participants) in the Yervoy monotherapy group.
CHECKMATE-017 TRIAL An Open-Label Randomized Phase III Trial of BMS-936558 (Nivolumab) Versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC) (The FDA-expanded use for metastatic squamous NSCLC was based on superior OS from the CheckMate-017 trial.)	This open-label, multicenter, multinational randomized trial allocated participants who had experienced disease progression while on or after receiving a platinum-based chemotherapy regimen to Opdivo (n=135) or docetaxel (n=137).	Patients were randomized 1:1 to receive Opdivo 3 mg/kg (n=135) or docetaxel 75 mg/m^2 (n=137).	Opdivo demonstrated improvement in OS as compared with docetaxel, with a median OS of 9.2 months for the Opdivo population and six months for docetaxel.
CHECKMATE-025 TRIAL A Randomized, Open-Label, Phase 3 Study of Opdivo (BMS-936558) vs. Everolimus in Subjects With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy	821 participants with advanced (clear-cell) renal cell carcinoma	Patients were randomized in a 1:1 ratio to receive Opdivo 3 mg/kg intravenously every two weeks or 10 mg of everolimus administered orally daily.	The primary endpoint for the study was OS. The median OS for the Opdivo group was 25 months vs. 19.6 months for the everolimus group.

Table 3: Available PD-1 Products[3,4]

Opdivo® (Nivolumab, Bristol-Myers Squibb)	Keytruda® (Pembrolizumab, Merck)
UNRESECTABLE OR METASTATIC MELANOMA **Indication:** Single agent for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma **Dosage:** 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity	UNRESECTABLE OR METASTATIC MELANOMA **Indication:** Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor **Dosage:** 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity
Indication: Single agent for the treatment of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma and disease progression following ipilimumab and a BRAF inhibitor **Dosage:** 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity	
Indication: With ipilimumab for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma **Dosage:** 1 mg/kg, followed by ipilimumab on the same day, every three weeks for four doses, then Opdivo 3 mg/kg every two weeks	
NON-SMALL CELL LUNG CANCER (NSCLC) **Indication:** Treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo **Dosage:** 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity	NON-SMALL CELL LUNG CANCER (NSCLC) **Indication:** Treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda **Dosage:** 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity
RENAL CELL CARCINOMA **Indication:** Treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy **Dosage:** 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity	

PD-1 Inhibitors *continued*

REFERENCES

1. Couzin FJ. Breakthrough of the year: Cancer immunotherapy. *Science.* 2013;342(6165):1432-1433.
2. Ascierto PA, Marincola FM. 2015: The year of anti-PD-1/PD-L1s against melanoma and beyond. *EBioMedicine.* 2015;2(2):92-93. **www.ebiomedicine.com/article/S2352-3964(15)00034-1/fulltext.** Accessed January 2016.
3. Opdivo prescribing information. Bristol-Myers Squibb. **www.opdivo.bmscustomerconnect.com/Gateway?TC=33889&utm_source=bing&utm_medium=cpc&utm_campaign=decision&utm_term=opdivo&utm_content=opdivogeneral_textad_gateway_text_tc33889.** Accessed January 23, 2016.
4. Keytruda prescribing information. Merck & Company. **www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.** Accessed January 25, 2016.
5. ClinicalTrials.gov website. **https://clinicaltrials.gov/ct2/results?term=PD1+&Search=Search.** Accessed January 28, 2016.
6. Guha M. The new era of immune checkpoint inhibitors. The Pharmaceutical Journal website. **www.pharmaceutical-journal.com/news-and-analysis/features/immune-checkpoint-inhibitors-bring-new-hope-to-cancer-patients/20067127.article.** November 18, 2014. Accessed January 26, 2016.
7. Mamalis A, Garcha M, Jagdeo J. Targeting the PD-1 pathway: A promising future for the treatment of melanoma. *Arch Dermatol Res.* 2014;306(6):511-519.
8. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol.* 2015;33(17):1974-1982.
9. Immune checkpoint inhibitors to treat cancer. American Cancer Society website. **www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/cancer-immunotherapy-immune-checkpoint-inhibitors.**
10. The PD-1 wave? Report says it's a $33B tsunami, with BMS surfing for first place. FiercePharmaMarketing website. **www.fiercepharmamarketing.com/story/pd-1-wave-report-says-its-33b-tsunami-bms-surfing-first-place/2015-03-04.** March 4, 2015. Accessed January 25, 2016.
11. Watkins N. FDA expands approval of BMS' Opdivo in combination with Yervoy for certain melanoma patients. Specialty Pharma Journal website. **www.spjnews.com/2016/01/fda-expands-approval-of-bms-opdivo-in-combination-with-yervoy-for-certain-melanoma-patients.** January 26, 2016.
12. What are the key statistics about melanoma skin cancer? American Cancer Society website. **www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-key-statistics.**
13. What are the survival rates for melanoma skin cancer, by stage? American Cancer Society website. **www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates.**
14. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 2015;372(26):2521-2532.
15. Yervoy prescribing information. Bristol-Myers Squibb.
16. NCI Dictionary of Cancer Terms. National Cancer Institute website. **www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=44067.**
17. Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination With Ipilimumab vs. Ipilimumab Alone in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma (CheckMate-069).
18. FDA approves Keytruda for advanced non-small cell lung cancer. U.S. Food and Drug Administration. News release. October 2, 2015. **www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465444.htm.**
19. FDA expands approved use of Opdivo to treat lung cancer. U.S. Food and Drug Administration. News release. March 4, 2015. **www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436534.htm.**
20. What are the key statistics about kidney cancer? American Cancer Society website. **www.cancer.org/cancer/kidneycancer/detailedguide/kidney-cancer-adult-key-statistics.** Accessed January 26, 2016.
21. Nivolumab (Opdivo) Medical Policy — Anthem. **www.anthem.com/medicalpolicies/policies/mp_pw_c180468.htm.** November 9, 2015. Accessed January 25, 2016.
22. Pembrolizumab (Keytruda) Medical Policy — Anthem. **www.anthem.com/medicalpolicies/policies/mp_pw_c176260.htm.** November 9, 2015. Accessed January 25, 2016.
23. Nivolumab (Opdivo) page. HealthPartners website. **www.healthpartners.com/public/coverage-criteria/nivolumab.** Accessed January 25, 2016.
24. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™. National Comprehensive Cancer Network website. **www.nccn.org/evidenceblocks.** Accessed January 25, 2016.
25. ASCO publishes conceptual framework to assess the value of new cancer treatment options. American Society of Clinical Oncology website. **www.asco.org/advocacy/asco-publishes-conceptual-framework-assess-value-new-cancer-treatment-options.** Accessed January 25, 2016.
26. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther.* 2015;14(4):847-856.
27. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature.* 2014;515(7528):568-571.
28. Goldstein DA, Zeichner SB. Strategies for individualizing management of patients with metastatic melanoma: A managed care perspective. American Journal of Managed Care website. **www.ajmc.com/journals/supplement/2015/ace0032_sep15_melanomace/ace0032_sep15_melanomace_goldstein_s234/P-1.** September 30, 2015.
29. KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, demonstrates superior survival, progression free survival and overall response rate compared to ipilimumab an anti-CTLA-4 therapy.... Merck. News release. April 19, 2015. **www.mercknewsroom.com/news-release/oncology-newsroom/keytruda-pembrolizumab-mercks-anti-pd-1-therapy-demonstrates-superior.** Accessed January 25, 2016.
30. Opdivo (nivolumab) first PD-1 inhibitor to demonstrate superior overall survival versus standard of care (docetaxel) in previously-treated non-squamous non-small cell lung cancer in pivotal phase III trial. Bristol-Myers Squibb. News release. May 29, 2015. **http://investor.bms.com/investors/news-and-events/press-releases/press-release-details/2015/Opdivo-nivolumab-First-PD-1-Inhibitor-to-Demonstrate-Superior-Overall-Survival-Versus-Standard-of-Care-docetaxel-in-Previously-Treated-Non-Squamous-Non-Small-Cell-Lung-Cancer-in-Pivotal-Phase-III-Trial.** Accessed January 25, 2016.
31. Rizvi N, Chaft J, Balmanoukian A, et al. Tumor response from durvalumab (MEDI4736) + tremelimumab treatment in patients with advanced non-small cell lung cancer (NSCLC) is observed regardless of PD-L1 status. Poster presentation. *J Immunother Cancer.* 2015;3(Suppl 2):P193.
32. U.S. FDA grants Breakthrough Therapy Designation for Roche's investigational cancer immunotherapy MPDL3280A (anti-PDL1) in non-small cell lung cancer. Roche. News release. February 2, 2015. **www.roche.com/media/store/releases/med-cor-2015-02-02.htm.** Accessed January 25, 2016.
33. Phase I/II Opdivo (nivolumab) trial shows Bristol-Myers Squibb's PD-1 immune checkpoint inhibitor is first to demonstrate anti-tumor activity in patients with hepatocellular carcinoma. Bristol-Myers Squibb. News release. May 29, 2015. **http://news.bms.com/press-release/phase-iii-opdivo-nivolumab-trial-shows-bristol-myers-squibbs-pd-1-immune-checkpoint-in.** Accessed January 25, 2016.
34. Clinically meaningful preliminary results with pembrolizumab in recurrent head and neck cancer. The ASCO Post website. **www.ascopost.com/issues/june-10-2015/clinically-meaningful-preliminary-results-with-pembrolizumab-in-recurrent-head-and-neck-cancer.** June 10, 2015. Accessed January 26, 2016.
35. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. *Lancet.* 2014;384(9948):1109-1117.
36. A study to compare BMS-936558 to the physician's choice of either dacarbazine or carboplatin and paclitaxel in advanced melanoma patients that have progressed following anti-CTLA-4 therapy (CheckMate-037). ClinicalTrials.gov website. **www.clinicaltrials.gov/ct2/show/NCT01721746?term=CHECKMATE+037&rank=1.** Accessed January 28, 2016.
37. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372(4):320-330.
38. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(1):23-34.
39. Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) (CheckMate-017). ClinicalTrials.gov website. **www.clinicaltrials.gov/ct2/show/NCT01642004?term=CheckMate-017&rank=1.** Accessed January 28, 2016.
40. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1803-1813.

NOW APPROVED

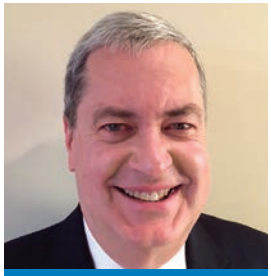
ZEPATIER™
(elbasvir and grazoprevir)
50 mg/100 mg tablets

For more information, visit **zepatier.com**.

MERCK

Understanding the Evolving Dynamics of Medical Pharmacy Expenditures

Tim Colligan, RPh, MS, Director Managed Care Pharmacy, Optima Health



Tim Colligan
RPh, MS

As health care costs continue to rise in the United States, managed care organizations (MCOs) are under a tremendous amount of pressure to contain the additional expenditures, while ensuring appropriate access to medical services and pharmacologic therapy, to remain competitive in the current insurance marketplace. One of the primary drivers of increased health care spend is the utilization of high-cost specialty pharmaceuticals. Although only accounting for approximately 1 percent of prescriptions, specialty medications represented nearly 32 percent of all drug spend in 2014.[1] With an additional 28 specialty pharmaceuticals approved for either cancer or rare diseases in 2015,[2] the increasing trend of specialty drug costs is expected to continue. Although many of these recently approved pharmaceuticals represent substantial scientific advances in the management of difficult-to-treat disease states, affordability of providing care is likely to be a growing concern in upcoming years.

To combat the escalation in specialty drug spend, MCOs are evaluating various opportunities to generate financial savings, with a focus on specialty drug utilization. However, before a solution can be developed, it is important to further examine the factors leading to potentially wasted costs and the true economics of specialty pharmaceuticals. Unfortunately, the economics of specialty medications are not as straightforward as those of traditional small molecule products. A major reason for this is the various delivery channels and the impact that these channels have on net product cost.

In general, the expense of specialty drugs is split 50/50 between medical and pharmacy benefits.[1] This alone adds complexity to the financial management of specialty drugs. Drug management under the medical benefit is often challenging for payors and is impacted by a number of different influences, including physician/hospital contracting, GPO-preferred products and discounts, and potential perverse incentives for physicians and outpatient hospitals to utilize more costly products.[3] The excessive expense associated with hospital outpatient utilization of physician-administered pharmaceuticals alone is enough for payors to evaluate cost-savings opportunities. The pharmacy benefit, however, is much more controllable for MCOs. The pharmacy benefit provides consistent and predictable pricing with easy-to-implement controls to drive the utilization of cost-effective products. Additionally, the economic influence on physician prescribing is mitigated under the pharmacy benefit. For these reasons, many MCOs are evaluating the opportunity to transition medical benefit products over to the pharmacy benefit. However, there are significant differences in the reimbursement models that are used between the two benefits, and it is important to consider the true economic impact resulting from driving utilization to a particular benefit.

Differences Between Medical and Pharmacy Reimbursement Models

Reimbursement under the pharmacy benefit is more straightforward when compared to medical drug reimbursement. As all managed care professionals know, the price of the drug is never actually the price of the drug. The first major difference is the pricing model that is used to reimburse pharmacologic products. Reimbursement under the pharmacy benefit is usually based on either average wholesale price (AWP) or wholesale acquisition cost (WAC), while much of the reimbursement

under the medical benefit is now based on average sales price (ASP). It is important to understand the differences between the various prices of each pharmacologic product.

For many years, AWP was accepted as a primary benchmark of drug payment for a multitude of payors; however, it is essentially the "sticker price" and does not reflect the average wholesale price that is actually paid after discounts are subtracted. WAC is the price that manufacturers establish for each product, and, similarly to AWP, WAC does not represent what a wholesaler actually pays for a drug following discounts and price concessions offered by manufacturers. WAC has become the primary starting point for negotiated discounts and rebates between manufacturers and private payors for both medical and pharmacy benefit products. As neither WAC nor AWP represent the true cost of pharmaceuticals, reimbursement under the pharmacy benefit is typically based on either a WAC minus (WAC-) or AWP minus (AWP-) model, where the health plan pays the pharmacy a pre-negotiated percentage below the WAC or AWP price. Commercial reimbursement rates to pharmacies are typically around AWP - 17 percent. It is important to remember that AWP is generally 20 to 25 percent higher than WAC.[4]

Under the medical benefit, however, ASP has largely replaced AWP-reimbursement models. ASP is based upon manufacturer-reported actual selling price data, which includes the majority of rebates, discounts, and other price concessions offered to all delivery channels and stakeholders. ASP has consistently proven to be substantially lower than AWP, and these values are publicly

Table 1: Comparison of WAC and ASP for High-Utilization Medical Benefit Products[5,6]

	AWP	WAC	ASP	ASP: Percent Below WAC
Remicade®, 100 mg (Infliximab)	$1,225.72	$1,021.43	$753.82	26%
Neulasta®, 6 mg (Pegfilgrastim)	$6,186.78	$5,155.65	$3,611.41	30%
Procrit®, 1,000 units (Epoetin alfa)	$26.77	$22.31	$11.63	48%
Aranesp®, 1 mcg (Darbepoetin alfa)	$8.94	$7.45	$3.92	47%

available on the Centers for Medicare & Medicaid Services (CMS) website, making these prices readily available for payors.[5] With this information now available, the majority of payors have transitioned medical benefit drug reimbursement to an ASP plus (ASP+) model. For example, Medicare Part B reimburses medical benefit drugs at ASP + 6 percent, or 106 percent of ASP[5] (commercial insurers typically reimburse ASP + 15 percent, on average). The transition to ASP+ reimbursement models has saved the U.S. health care system billions since their inception in 2005. Unfortunately, ASP is not available for pharmaceutical products immediately upon approval. ASP is based on a calculation of volume and discounts, so it typically takes six to nine months before ASP is available for newly approved products, and once available, changes quarter to quarter.

It is also important to understand how these various price points change over time. Although there may be a few exceptions, manufacturers typically increase the WAC of pharmaceutical products over time, with some specialty products taking multiple price increases annually. Unfortunately, payors are unable to control price increases, outside of price protection contracts, which typically allow for minimal increases in price. The impact, however, that this has on ASP is interesting. In general, the longer a product is available on the market, the greater the discounts. This creates a steadily increasing difference between WAC and ASP as time progresses. A simple evaluation of current WAC and ASP for frequently used medical benefits products helps to put this concept into perspective (Table 1).

Some managed care organizations have considered, and even implemented, initiatives designed to transition Remicade® (infliximab) to the pharmacy benefit, the primary reason being the high cost associated with hospital outpatient utilization. For many plans, the reimbursement of Remicade when administered in a hospital outpatient setting is upwards of ASP + 200 percent, compared with ASP + 15 percent when administered in an independent physician office or infusion center. However, it is extremely challenging for payor organizations to implement "Specialty Pharmacy Only" policies on their network hospitals and these initiatives are often unsuccessful. In fact, most of the pharmacy utilization would most likely be diverted from private physician offices resulting in an increased overall spend.

A recent analysis of Remicade within a regional health plan can also help estimate the difference in net cost of Remicade if 100 percent of the physician office utilization was transitioned to the pharmacy benefit.[7] In this specific health plan, which represented approximately 2.8 million commercial lives, a total of 450,000 units (10 mg) were administered in the outpatient physician office setting over a 12-month period. This resulted in a total of just over $33 million spent on Remicade, or an average of $73.50 per unit (average reimbursement of ASP + 10 percent in Q1 2014). If this utilization was transitioned to the pharmacy benefit using an AWP - 17 percent reimbursement model, it would result in a reimbursement rate of $101.73 per unit, or an additional cost of nearly $12.7 million.

Table 2: Remicade Cost/Unit by Site of Care[6]

	Reimbursement Rate	Cost per Unit (10 mg)
Hospital Outpatient	ASP + 200%	$226.14
Specialty Pharmacy	AWP - 17%	$101.73
Home Infusion	ASP + 26%	$94.98
Physician Office	ASP + 13%	$85.18

Although hospital outpatient administration remains the site of care associated with the greatest cost, specialty pharmacy utilization is generally the next most expensive site of care. When developing cost-saving initiatives for medical benefit products, it may be more economically impactful to develop strategies to transition utilization from the hospital outpatient facilities to independent physician practices, the least-expensive site of care, rather than the pharmacy benefit. Additionally, removing the option to "buy and bill" is likely to have a negative impact on physician satisfaction and increase network disruption.

When reviewing pharmacologic products for benefit allocation, it may be worthwhile to remember the following characteristics that make pharmaceuticals good candidates for the medical benefit:

- Able to adjudicate under the medical benefit (e.g., available J-code)
- Significant difference between ASP and WAC
- Infusible

Economic Evaluation of Future Medical Benefit Biosimilar Therapies

For the past several years, there has been an abundance of discussion around the cost-savings potential of biosimilar products. However, managed care organizations have not yet been able to enjoy these financial benefits. In 2015, the first biosimilar was approved and made available, Zarxio™ (filgrastim-sndz, by Sandoz). Unfortunately, this product was a bit anticlimactic from the managed care perspective. Although a medical benefit biosimilar product to compete with Neupogen® (filgrastim, by Amgen) in the G-CSF class, the majority of the outpatient utilization in this class had already been converted to Neulasta® (pegfilgrastim, by Amgen), making the savings potential for payors minimal.

Therefore, the potential for biosimilar products to provide cost-saving opportunities for payors is still on the horizon. However, the economics of biosimilars is much more complex

than it may initially appear, especially for products that will be managed under the medical benefit (i.e., pegfilgrastim, infliximab, etc.). When reviewing the financial opportunity associated with biosimilar products, it is important to consider all of the following:

Price point compared to the reference product: How does the WAC of the biosimilar compare to the WAC, ASP, and the plan's net price (including rebates/discounts) for the reference product? This will help to understand the true savings potential.

Reimbursement prior to ASP availability: Until ASP is available, biosimilars will be reimbursed based on WAC pricing. Depending on the initial price point, this could actually make biosimilars more expensive compared with reference products for the first six to nine months — especially for reference products with a large difference between WAC and ASP.

Ability to drive market share: This could be largely dependent on the type of condition for which the product will be used. It may be easier to drive market share for acute products, such as oncology supportive care products, compared with chronic therapies such as infliximab. Physicians may be hesitant to switch stable patients that are on chronic therapy, hence, grandfathering active patients may be required. This will have a significant impact on the ability to maximize biosimilar market share. Additionally, the amount of work/resources that is required to drive biosimilar market share, including outreach/education to network providers, needs to be considered.

Loss of reference product medical rebates: To remain competitive against biosimilar entrants, reference product manufacturers will be more likely to entertain medical rebate offerings. This must be considered during the cost-savings analysis to assess the net savings impact.

Fee schedule management: To ensure market share optimization, plans may have to modify their physician fee schedule to incentivize physicians to prescribe cost-effective biosimilars. Increasing reimbursement to physicians may cut into the net savings for health plans.

Shared J-code: All biosimilars for the same reference product will share the same J-code. This makes it difficult to differentiate individual products in medical claims data, which may be problematic when evaluating exclusive contracting opportunities.

Biosimilars have the potential to save the U.S. health care system billions of dollars over the next few decades, but only if these products can obtain widespread adoption and acceptance by payor organizations. The responsibility to provide a cost-saving opportunity certainly falls on the shoulders of the biosimilar manufacturers, but it is important for payors to evaluate opportunities within their own organizations and physician networks to optimize utilization of these cost-effective products to maximize these savings. By having a strong understanding of the major factors influencing the economic viability of biosimilar products, managed care organizations will have the ability to make practical assessments of the true savings potential within their own health plans.

REFERENCES

1. The Express Scripts Lab. The Express Scripts 2014 drug trend report. **http://lab.express-scripts.com/~/media/PDFs/Drug%20Trend%20Report/ExpressScripts_DrugTrendReport.ashx.** March 2015. Accessed January 19, 2016.
2. U.S. Food and Drug Administration. Novel drugs 2015 summary. **www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM481709.pdf.** 2016. Accessed January 19, 2016.
3. Magellan Rx Management. Magellan Rx Management medical pharmacy trend report. **https://www1.magellanrx.com/magellan-rx/publications/medical-pharmacy-trend-report.aspx.** 2015(6). Accessed January 19, 2016.
4. AWP Policy. Truven Health Analytics, Micromedex Solutions website. **http://micromedex.com/awp-policy.** October 1, 2014. Accessed January 19, 2016.
5. Medicare Part B drug average sales price. Centers for Medicare & Medicaid Services website. **www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html.** March 30, 2015. Accessed January 19, 2016.
6. Red Book Online. Truven Health Analytics. **www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/24C711/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/7AB5B7/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/redbook.FindRedBook?nav.** 2016. Accessed January 19, 2016.
7. Leo S, Lord T, Hassan K, et al. Real world analysis of the economic impact of infliximab utilization by site of care and medical diagnosis within two regional health plans. Magellan Rx Management. Newport, RI. AMCP Nexus, 2014.

Cost Considerations in Managing Age-Related Macular Degeneration

Kimberly Dornbrook-Lavender, PharmD, BCPS, Manager, Formulary Strategy & Clinical Programs, Medica; Johanna Melendez, PharmD, Director, Formulary Rebate & Specialty Pharmacy, EmblemHealth

Kimberly Dornbrook-Lavender
PharmD, BCPS

There are two primary types of age-related macular degeneration (AMD), dry (atrophic) and wet (neovascular or exudative).[1] In "dry" AMD, yellowish deposits, called drusen, form under the retina during the aging process. Increases in drusen size and number lead to a slow deterioration of the macula, resulting in a gradual loss of vision over a period of years. In some people, this causes distorted central vision and decreases in near and far vision.[1]

In about 10 percent of cases, dry AMD will progress to wet AMD.[1] Neovascular AMD — often called "wet" macular degeneration — is the more advanced type of AMD. It affects approximately 10 to 15 percent of people with AMD, but accounts for 90 percent of the severe vision loss caused by AMD.[2] Neovascular AMD is marked by abnormal choroidal neovascularization (CNV) and vascular leak, leading to a centrally blinding disciform scar that can profoundly impair visual acuity.[1] The development of these abnormal blood vessels is due in part to the activity of vascular endothelial growth factor (VEGF), a diffusible cytokine that stimulates angiogenesis and increases vascular permeability and inflammation.[3] These vascular changes are believed to contribute to progression from dry AMD to wet AMD.[1]

AMD affects as many as 15 million Americans, with 200,000 new cases identified each year.[4] Figure 1 shows age-specific prevalence rates for all types of AMD. The main risk factors associated with the development of advanced AMD are increasing age, ethnicity, and genetics. White Americans have the greatest likelihood of developing AMD as compared with people of other races, but incidence is growing rapidly among Hispanics.[5] Cigarette smoking is the main modifiable risk factor that has been consistently identified in the medical literature; therefore, smoking cessation is strongly recommended for patients who have, or are at risk for, AMD.[6]

Treatment Landscape

Prospective randomized controlled clinical trials support the use of antioxidant vitamins and minerals for slowing progression to later stages of AMD. In the initial study of supplementation, Age-Related Eye Disease (AREDS), 3,640 participants were randomized to treatment with either antioxidant vitamins, minerals, a combination of antioxidant vitamins plus minerals, or a placebo and were followed for a mean of six years.[7] A subsequent study, AREDS2, enrolled 4,203 participants with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye.[8] This population represented a high-risk group for progression to more advanced states of AMD. The study modified some of the supplements and dosing used from those in the original AREDS study. Upon completion of AREDS2, researchers at the National Eye Institute recommended adjusting the original AREDS formula to remove beta-carotene, and add lutein and zeaxanthin, to the zinc, copper, and vitamins E and C administered in the original study.[7,8]

In both the AREDS and AREDS2 studies, participants who benefited from antioxidant vitamin and mineral supplementation were those who had either intermediate AMD or advanced AMD in one eye. The therapy that resulted in a statistically significant reduction in both the development of advanced AMD and vision loss was the combination treatment of antioxidant vitamins and the minerals zinc and copper.[7,8] Based on this data, the American Academy of Ophthalmology recommends practitioners consider antioxidant vitamin and mineral supplementation in patients with intermediate or advanced AMD. There is no evidence to support use of these supplements for patients who have less than intermediate AMD.[6]

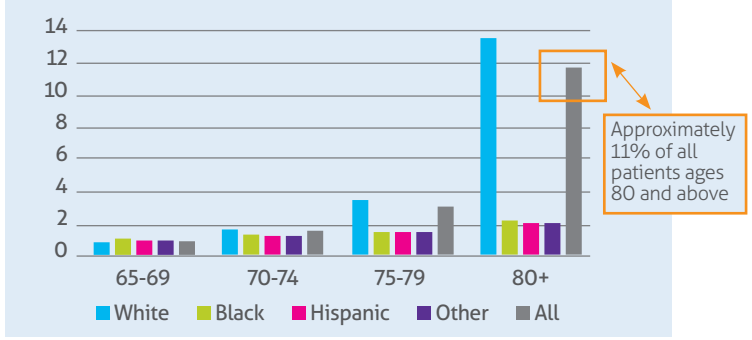
Anti-VEGF Therapies

Blockade of VEGF has become first-line therapy for treating and stabilizing most cases of neovascular AMD.[6] Anti-VEGF injections promote regression of the abnormal blood vessels that develop during neovascular AMD, helping to improve vision. Macugen® (pegaptanib), Lucentis® (ranibizumab), Eylea® (aflibercept), and Avastin® (bevacizumab) are used in the treatment of neovascular AMD (see Table 1).[9]

Bevacizumab, aflibercept, and ranibizumab have not only revolutionized the treatment of AMD, but these treatments are also effective in other retinal diseases, such as diabetic macular edema (DME), which is a consequence of diabetic retinopathy.[10] Diabetic retinopathy affects blood vessels in the retina, which is the most common cause of vision loss among diabetics.[10] Bevacizumab was first investigated as an intravenous treatment for AMD and then as an intravitreal injection prior to FDA approval of ranibizumab. Based on preliminary reports, ophthalmologists began to use intravitreal bevacizumab off-label to treat CNV, with some success reported for improvements in visual acuity and decreased retinal thickness following treatment.[6] Table 2 delineates the key findings from selected randomized controlled trials of CNV treatment.

The Comparison of AMD Treatment Trial (CATT) was a multicenter clinical trial that described the effects of ranibizumab and bevacizumab when administered monthly or as needed for one year and the impact of switching to as-needed treatment after one year of monthly treatment. For

Figure 1: U.S. Age-Specific Prevalence Rates for AMD by Age and Race/Ethnicity (Percent)[5]



2010 U.S. age-specific prevalence rates for AMD by age and race/ethnicity. The risk of AMD increases with age. The disease is most common among older white Americans, affecting more than 14 percent of white Americans ages 80 and older, based on 2010 data.[5]

Table 1: Available Treatments for AMD[9]

Brand	Generic	Maintenance Dose and Frequency (AMD)	Cost/Dose (ASP††† + 6%)	Annual Cost/Eye
Avastin	bevacizumab	1.25 mg monthly	$70.96††	$851.52
Eylea	aflibercept	2 mg every eight weeks†	$1,961.00	$13,727.00
Lucentis	ranibizumab	0.5 mg monthly	$1,931.67	$23,180.04
Macugen	pegaptanib	0.3 mg every six weeks	$1,054.70	$9,492.30

†*After loading dose schedule is completed, 2 mg every 4 weeks x 3 doses* ††*J9035* †††*ASP 4/1/16 rates*

Table 2: Key Findings from Selected Randomized Controlled Trials of CNV Treatments

Study	Number of Patients and Study Duration	Dosing	Primary Endpoint	Results
CATT bevacizumab (Avastin) vs. ranibizumab (Lucentis) injection[11]	N=1,208 1 year	Bevacizumab or ranibizumab injections monthly or PRN	Mean change in visual acuity at 1 year	Bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same regimen. Bevacizumab and ranibizumab had the same safety and efficacy profiles.
MARINA Study Group ranibizumab (Lucentis)[12]	N=716 2 years	Ranibizumab (0.3 mg or 0.5 mg) or sham injections monthly	Proportion of patients losing < 15 letters at 12 months	94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost < 15 letters over 12 months vs. 62.2% of patients receiving sham injections.
ANCHOR ranibizumab (Lucentis)[13]	N=423 2 years	Ranibizumab (0.3 mg or 0.5 mg) + verteporfin (Visudyne®) therapy or sham injections + verteporfin therapy given monthly	Proportion of patients losing < 15 letters from baseline visual acuity at 12 months	94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost < 15 letters vs. 64.3% in the verteporfin group.
VIEW 1 and 2[14] aflibercept (Eylea) vs. ranibizumab (Lucentis)	N=2,419 1 year	Aflibercept 0.5 mg monthly, 2 mg monthly, or 2 mg every two months after three initial monthly doses, or 0.5 mg ranibizumab monthly (Rq4)	Noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing < 15 letters on ETDRS chart)	The proportion of patients maintaining vision was similar among all treatment groups. All aflibercept groups were noninferior and clinically equivalent when compared to monthly ranibizumab. (Ranibizumab 94.4% maintained vision in both studies; for aflibercept in VIEW 1: 2q4, 0.5q4, and 2q8 regimens, vision maintenance was reported in 95.1%, 95.9%, and 95.1%, respectively, and, VIEW 2, 95.6%, 96.3%, and 95.6%.)

patients placed on the same regimen for two years, the mean gain in visual acuity was similar for both drugs. There was a statistical difference in visual acuity gains when patients were on a monthly regimen versus an as-needed regimen. When patients were switched from monthly to as-needed treatment after year one, mean change in visual acuity was similar for both drugs.[15] Based on clinical trial data, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.[7] In addition, bevacizumab and ranibizumab had the same safety and efficacy profiles.[15]

Additional research in AMD includes a study demonstrating ranibizumab prevented vision loss and improved mean visual acuity in two randomized controlled trials.[12,13] Based on these results, the FDA approved ranibizumab for treatment of neovascular AMD in 2006.[16] A newer therapeutic agent, aflibercept, was reported to be equivalent in efficacy to ranibizumab in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD trials (VIEW Study). In these studies, aflibercept was initially administered monthly for three months, followed by injections every four weeks and every eight weeks.[14]

Pegaptanib was the first anti-VEGF agent available for treating neovascular AMD. Unlike other approved agents, pegaptanib does not improve visual acuity, on average, in patients with new-onset neovascular AMD and is rarely used.[6]

Other Treatments

In addition to injection of VEGF inhibitors, verteporfin (Visudyne) photodynamic therapy (PDT) is an approved option for the treatment of subfoveal lesions of AMD. This therapy is rarely needed but may be used in patients who do not respond to anti-VEGF therapy.[6] Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment.[6]

Economic Considerations

The availability of anti-VEGF therapy for neovascular AMD has prevented or delayed blindness in many individuals. For these people, placing a dollar value on vision is inconceivable. Yet, the significant costs associated with AMD to the health care system as a whole and to individual health plans warrant serious consideration of an AMD management strategy. With ASP-based pricing, providers are discouraged from using cost-effective pharmaceutical alternatives, such as bevacizumab, and are incentivized to administer higher-cost products.

In a recent article published online by *The Washington Post*, Andrew Lam, MD, a retinal surgeon and assistant professor at Tufts University School of Medicine, expressed that although bevacizumab, aflibercept, and ranibizumab are effective therapies in the treatment of AMD, these products have become controversial due to the significant differences in cost.[17] Medicare covers these products; however, a recent survey given to retinal specialists revealed that 64.3 percent use bevacizumab as first-line therapy, while the remaining 35 percent continue to use the more expensive products, aflibercept and ranibizumab, as first-line therapy.[17] While Dr. Lam feels those providers are most likely prescribing the more expensive products because they feel they are slightly better than bevacizumab, this does raise an ethical issue for providers, who must weigh what they feel is best while also remaining fiscally responsible through the recommendation of cost-effective care. Also, there is a financial incentive for providers to prescribe more expensive products because Medicare reimburses physicians approximately 4 percent more than the cost of drugs administered.[17] A 2014 Health Affairs study delineated that Medicare and American taxpayers could save $18 billion over the next 10 years if providers switched to the more cost-effective therapy, bevacizumab.[17] However, in a health care system with limited resources, the opportunity to utilize a therapy that costs approximately $50 versus alternatives that cost approximately 40 times more is not only impactful but could generate savings that could be allocated toward other disease states. Dr. Lam concluded that while providers should still have the opportunity to prescribe all three treatments with patients, they should consider the impact of their product choices on the health care system.

An analysis of payor claims from 2014 showed bevacizumab is utilized in the treatment for a majority of Medicare AMD patients.[9] This dynamic might be driven by benefit design, as Medicare beneficiaries are typically financially liable for a 20 percent coinsurance for medical benefit drugs. Within the Medicare population, bevacizumab was utilized by 64 percent of members versus 26 percent for Lucentis and 10 percent for Eylea.[9] The annual cost per patient for bevacizumab was $228, compared with $9,164 for Lucentis and $8,307 for Eylea.[9] Lastly, the PMPM was $0.18 for bevacizumab, compared with $0.89 for Eylea and $2.76 for Lucentis.[9] Within the commercial health plan population, Lucentis represented the largest spend; however, bevacizumab was utilized by a larger portion of members: 55 percent of members utilized bevacizumab, 32 percent utilized Lucentis, and 13 percent utilized Eylea.[9] Bevacizumab had an annual cost per patient of $202, compared with $8,052 for Eylea and $7,016 for Lucentis.[9] In addition, the bevacizumab allowed amount PMPM was $0.01, representing a blended annual cost for all uses including oncology and retina diseases, compared with $0.08 for Eylea and $0.17 for Lucentis.[9]

Based on data provided by the Agency for Healthcare Research and Quality (AHRQ), the total direct medical costs associated with AMD and cataracts, plus the related expected costs of post-procedure nursing care/assisted living services, approached $17 billion among all U.S. adults over the age of 55 in 2012.[18] Consistently, the evidence shows that since the approval of VEGF inhibitors, patients with neovascular AMD have costs many times greater than those with early stages of the disease.[19]

Although data regarding the costs of AMD specifically to managed care payors is lacking, the direct costs of any-cause blindness for patients enrolled in managed care in the first year of follow-up have been reported to be significantly higher than those for non-blind patients: $20,677 versus $13,321.[20] Given the aging of the American population, an exponential increase in the number of people afflicted with AMD is anticipated. It is estimated that the prevalence of AMD will increase to 3.6 million by the year 2030.[5] The economic impact of AMD on payors, therefore, can be expected to increase substantially in the years ahead.

On a microeconomic level, the burden of anti-angiogenic therapy to the patient can be considerable. Under Medicare benefit design, physician-administered drugs are covered as a Part B benefit, leaving patients responsible for 20 percent of costs for the drug and physician services for drug administration. In a study assessing costs of treatment with ranibizumab and aflibercept, total drug costs for the member were estimated at approximately $400 to $500 per injection. It is estimated that six injections of ranibizumab administered over the course of one year would result in approximately $13,636 in overall treatment costs (including office visits, medical appointments, drug costs and administration, and angiography testing). Of these costs, Medicare patients may be responsible for 20 percent, or approximately $2,727 in out-of-pocket expenses.[21] There are copayment assistance programs for patients who financially qualify to reduce out-of-pocket costs; however, the cost of health care remains the same.

Many ophthalmologists recognize an obvious way to decrease the cost of anti-VEGF therapy is to use less expensive drugs, such as off-label bevacizumab. It is estimated that converting all ocular anti-VEGF treatments to bevacizumab would save the U.S. health care system $29 billion over the next decade.[22] In addition, ophthalmologic use of bevacizumab and ranibizumab has increased and now accounts for approximately one-sixth of the Medicare Part B drug budget.[22]

Opportunities for Managing AMD Costs

Because the drug costs associated with AMD are not of the same magnitude as other disease states such as oncology, they are often overlooked. Managed care organizations generally do not aggressively review this category of drugs, partially due to a lack of published payor-oriented studies on ophthalmologic agents. Although the drugs have similar efficacy and safety profiles, the cost differential is substantial. A recent analysis proposes ranibizumab costs *40 times more* than bevacizumab.[22]

However, a discussion of the economics of AMD therapies would be incomplete without consideration of product packaging and availability. Ranibizumab is available in ready-to-use vials from the manufacturer, at approximately

$2,000 per dose. Bevacizumab, at $70 per dose, is packaged in large vials, intended for cancer treatment. It must be compounded into smaller doses for treatment of wet AMD.[23] The compounding requirement for bevacizumab has raised questions regarding potential sterility issues and the risk of infections. In response to these questions, researchers analyzed more than 296,000 injections of bevacizumab and more than 87,000 injections of Lucentis, and they found the rates of serious eye infection were 0.017 percent for bevacizumab and 0.025 percent for Lucentis.[23] In addition, the FDA has placed strict 503B regulations for compounding pharmacies that outsource bevacizumab. They must comply with Current Good Manufacturing Practice (CGMP) requirements and FDA inspections and must meet certain other conditions to ensure quality and safety.[24]

Additional Considerations for Managed Care

Anti-VEGF injections are costly for both payors and patients. Plans should consider clinical management programs to help manage the treatment of AMD, with the objective of managing the largely untapped potential for cost-savings within this drug category. During the creation of a program, health plans should also consider highlighting the clinical and economic benefits of bevacizumab. This may also involve adjustments to physician reimbursement to remove the disincentive from using cost-effective therapies when clinically appropriate.

Beyond reducing drug spend, disease management strategies can improve health outcomes by helping payors reduce the overall cost burden associated with AMD. The costs associated with dry AMD are reported to be half of wet AMD.[19] Delaying progression of dry AMD or initiating programs to eliminate risk factors, such as smoking, could lead to further substantial reduction in payor costs.[19]

Looking to the future, comparative effectiveness and cost-effectiveness studies will contribute to the understanding of treatments, providing the best outcomes for patients at the lowest cost. Additionally, programs that encourage adherence and promote medical follow-up can also improve outcomes. Ophthalmic drug formularies of managed care plans may need to permit greater flexibility in prescribing practices to support attainment of optimal clinical and economic outcomes.[25] By removing financial incentives for providers to prescribe more costly drugs and educating clinicians about efficacy and outcomes across agents, payor programs can encourage cost-conscious and clinically effective prescribing patterns.

REFERENCES

1. Hageman GS. Age-related macular degeneration (AMD). Webvision website. **www.webvision.med.utah.edu/book/part-xii-cell-biology-of-retinal-degenerations/age-related-macular-degeneration-amd.** 2015. Accessed December 11, 2015.
2. Wet AMD. Macular Degeneration Partnership website. **www.amd.org/what-is-macular-degeneration/wet-amd.** 2015. Accessed December 11, 2015.
3. Barak Y, Ihnen MA, Schaal S. Anti-vascular endothelial growth factor pharmacotherapy in the treatment of subretinal choroidal neovascularization. *US Ophthalmic Rev.* 2012;5(2):107-110.
4. Age-related macular degeneration. American Society of Retina Specialists website. **www.asrs.org/patients/retinal-diseases/2/agerelated-macular-degeneration.** Accessed November 18, 2015.
5. Age-related macular degeneration (AMD). National Eye Institute website. **https://nei.nih.gov/eyedata/amd#1.** Accessed November 18, 2015.
6. Age-related macular degeneration PPP. American Academy of Ophthalmology website. **www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp-2015.** 2015. Accessed November 18, 2015.
7. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119(10):1417-1436.
8. Chew EY, SanGiovanni JP, Ferris III FL, et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. *JAMA Ophthalmol.* 2013;131(7):843-850.
9. Magellan Internal Data. *2015 Medical Pharmacy Trend Report*™.
10. Facts about diabetic eye disease. National Eye Institute website. **https://nei.nih.gov/health/diabetic/retinopathy.** September 2015. Accessed January 25, 2016.
11. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364(20):1897-1908.
12. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1432-1444.
13. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
14. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology.* 2012;119(12):2537-2548.
15. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology.* 2012;119(7):1388-1398.
16. FDA approves new biologic treatment for wet age-related macular degeneration. U.S. Food and Drug Administration. News release. June 30, 2006. **www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108685.htm.** Accessed December 11, 2015.
17. Lam A. Why do doctors choose a $2,000 cure when a $50 one is just as good? *The Washington Post.* December 10, 2015. **www.washingtonpost.com/news/wonk/wp/2015/12/10/why-do-doctors-choose-a-2000-cure-when-a-50-one-is-just-as-good.** Accessed January 22, 2016.
18. Shanahan C, de Lorimier R. Age-related eye disease and the cost effectiveness of using lutein and zeaxanthin. *Smart Prevention — Health Care Cost Savings Resulting from the Targeted Use of Dietary Supplements.* Frost & Sullivan. 2013.
19. Schmier JK, Levine JA. Economic impact of progression of age-related macular degeneration. *European Ophthalmic Review.* 2013;6(1):52-57.
20. Frick KD, Walt JG, Chiang TH, et al. Direct costs of blindness experienced by patients enrolled in managed care. *Ophthalmology.* 2008;115(1):11-17.
21. Shah AR, Williams GA. Regulatory and economic considerations of retinal drugs. *Dev Ophthalmol.* 2016;55:376-380.
22. Hutton D, Newman-Casey PA, Tavag M, Zacks D, Stein J. Switching to less expensive blindness drug could save Medicare Part B $18 billion over a ten-year period. *Health Aff (Millwood).* 2014;33(6):931-939.
23. VanderBeek BL, Bonaffini SG, Ma L. Association of compounded bevacizumab with postinjection endophthalmitis. *JAMA Ophthalmol.* 2015;133(10):1159-1164.
24. Outsourcing facilities. U.S. Food and Drug Administration website. **www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm.** 2015. Accessed January 29, 2016.
25. Cardarelli WJ, Smith RA. Managed care implications of age-related ocular conditions. *Am J Manag Care.* 2013;19(5 Suppl):S85-91.

Health Economics and Outcomes Research for Health Plan Decision-Makers

Rusty Hailey, PharmD, MBA, FAMCP, Chief Pharmacy Officer, State of Tennessee Division of Health Care Finance and Administration; Michael Polson, MS, PharmD, Director HEOR, Magellan Rx Management

Health Economics and Outcomes Research (HEOR) is a term used to describe research with the goal of supplementing traditional clinical development research (phase 1–4). This type of research looks to guide health care decision-makers on the impact of an intervention in support of patient access. HEOR can span a variety of different methodologies with the ultimate goal of helping payors determine whether an intervention or treatment works on a population level and guide reimbursement decisions.[1] Pharmaceutical manufacturers conduct a majority of HEOR to supplement the evidence derived from clinical trials, often using real-world data to evaluate the outcomes or the economic impact associated with their products.

Rusty Hailey
PharmD, MBA, FAMCP

However, interest in HEOR has been growing in the payor segment as well. A recent survey showed approximately 75 percent of pharmacy and therapeutics decision-makers incorporate HEOR data into the formulary decision process, and more than 80 percent state they will use HEOR in the future.[1] In addition to incorporating the results from HEOR studies into their formulary review process, increasingly more payors are interested in utilizing their medical data, pharmacy data, and electronic medical records (if available) to conduct their own HEOR studies. This research helps payors understand the real-world clinical and economic impact of medications or specific interventions within their coverage network and can help promote informed decision-making.

Michael Polson
MS, PharmD

The intent of this article is to help payor organizations evaluate HEOR studies. For organizations interested in conducting their own HEOR studies, this article will describe some common study methodologies and highlight the important implications from each.

Budget Impact Analysis

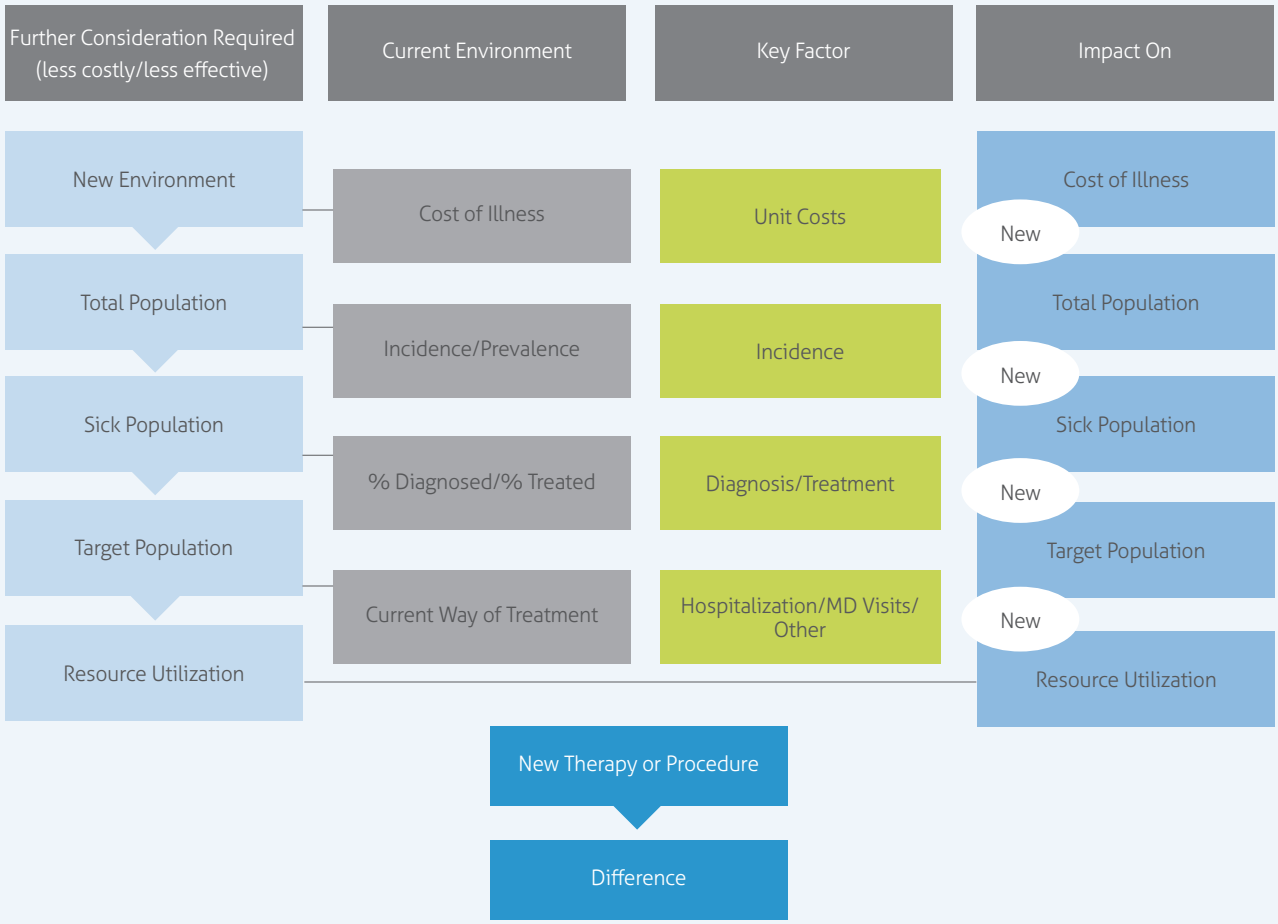
A budget impact analysis (BIA) utilizes available data to estimate the financial consequences of incorporating a product or treatment regimen into a health care system. The purpose for the analysis should be to develop a framework that allows decision-makers to incorporate local input values and tailor the analysis in a model to their individual plan or system population.[2]

An important portion of the BIA is the identification of the target population. Often, it may be difficult to identify how many patients may be part of the eligible population, and the BIA is an important tool to help estimate the target population. Furthermore, if disease severity is an important feature of the intervention, the BIA may provide variation of the impact stratified by disease severity, which could be helpful if there are treatments with shorter or longer duration.

Often, different scenarios are incorporated into the analysis, starting with a base case scenario of the most likely population, comparing the current interventions at baseline for the eligible population and the expected uptake of the new intervention.[2] Three scenarios may potentially be considered, one where the new intervention:

- Replaces one or more of the current interventions
- Is added to the current interventions
- Is used where there was no active intervention[2]

Figure 1: Overview of Budget Impact Framework[2]



Time horizons for BIAs should be of relevance to your health plan, normally between one and five years. Additionally, an appropriate sensitivity analysis should be included that helps identify the impact on some parameters of uncertainty.

When looking at results of a BIA, it is important to look at the table of assumptions and identify which (if any) assumptions could be modified for your local plan population. Typically, a BIA results section will include the budget impact compared to baseline, which could include the impact of resource utilization, adverse events, and the pharmacy budget. Incorporating total costs of care on the pharmacy budget can provide a more complete picture of the overall budget impact.

The BIA (Figure 1) is a simple tool that provides a short-term look at the budget impact to your health plan and incorporates different scenarios that are more applicable to their specific plan population. When you have products that are relatively similar with limited clinical and safety differentiation, the BIA can be an important starting point when making health care decisions.

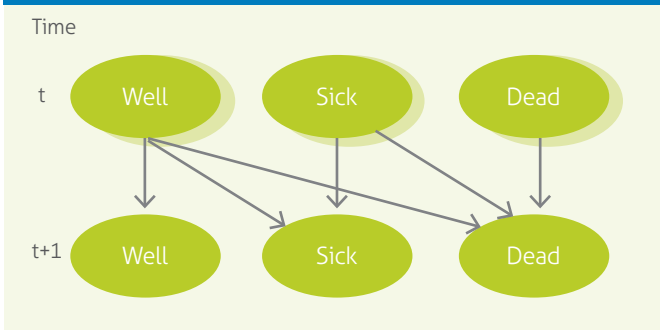
Cost-Effectiveness Analysis

A cost-effectiveness analysis (CEA) often accompanies a BIA. The CEA provides a different lens on the impact of an intervention. While the BIA generally considers only the impact on budget, the CEA incorporates measures of efficacy and/or quality of life. CEAs are important to consider in a therapeutic area where products have differentiation or nuances related to clinical, humanistic, and economic outcomes. To understand the ultimate goal of a CEA, it's important to first understand the incremental cost-effectiveness ratio (ICER). The ICER represents the relative cost per unit of effectiveness in switching from A to B of the following formula:

$$\text{ICER} = \frac{\text{Cost A - Cost B}}{\text{Effectiveness A - Effectiveness B}}$$

While the formula is simple, the complexity comes in the identification of the appropriate inputs for each of these data sets and the interpretation of the ICER. CEA models

Figure 2: Simple Markov Model



Source: Costs and cost determination. Decision modeling techniques. Markov modeling in decision analysis. **http://intranet.tdmu.edu.te.ua/data/kafedra/internal/upr_ekon/classes_stud/en/pharm/prov_pharm/ptn/Pharmacoeconomics/4/2%20Costs%20and%20cost%20determination.%20Modeling%20Techniques.htm.** Accessed January 15, 2016.

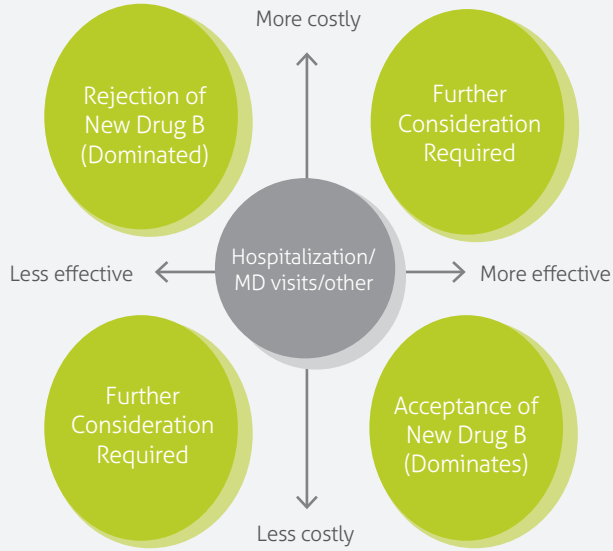
compare the effectiveness of each model comparator in treating the disease in question, and therefore must include an appropriate model that can capture the disease process. Often this is done through a Markov-simulation model, which is a model that looks at what state (sick/well, stage I/stage II) a person is in at different points in time (Figure 2).

A model needs to be simple enough to be understood, yet complex enough to capture the appropriate inputs. When there is a disease with chronic implications, a Markov model can incorporate multiple different disease states and model this information over time. Thus, a patient starts at a set disease state and transitions to the next disease state based on a rate identified in the literature. Each disease state incurs a cost and quality measurement, which presumably may be different based on treatment interventions. Often, the quality-adjusted life year (QALY) is incorporated, which is an approach at a universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programs. A QALY combines, in a single measure, gains or losses in both quantity of life (mortality) and quality of life (morbidity).[3] Results from the ICER are typically presented as a cost per QALY (e.g., $80,000 per QALY), which can be plotted in the cost-effectiveness space diagram (Figure 3).

To interpret the diagram, in the lower left space, the treatment is less costly but also less effective. This scenario warrants further review to determine the cost-effectiveness of the particular product. In the lower right space, the new treatment is more effective and less costly. The scenario is referred to as dominance; the new treatment dominates over the old. In the upper left-hand quadrant the new drug is less effective and more costly than previous products and thus is dominated by the previous therapies. The more common scenarios are seen in the upper right and lower left quadrants, in which the new treatment is more costly and more effective or less costly and less effective, respectively.

In the United States, a number that has become accepted as the number above which treatments are not cost-effective is the $50,000/QALY number. There is no real basis for this cutoff. It comes from a 1984 paper that evaluates renal-replacement therapy/dialysis, in which the ICER was $50,000/QALY in Canadian dollars.[4] It's important to recognize not all modeling studies and interventions are created equal. When comparing data from one CEA versus another, it is important to look at the underlying assumptions of the analysis. For example, one CEA may model outcomes over 10 years versus another looking at a lifetime, resulting in significant differences in the outcomes of interest (e.g., cost per QALY). Additionally, the comparator regimens are important. An analysis may compare the comparator of interest to supportive treatment instead of an active comparator, resulting in significant differences in the outcome of the analysis. It should be recognized that when a clinical trial is utilized to populate the efficacy parameter in a model, the outcome could be significantly different than what is seen in the real world. In the comparison of two clinical trials, often significant differences in baseline severity exist, which may have a lasting impact on the outcome of a modeling study. When evaluating the results of an analysis, understanding the population of the clinical trials and recognizing differences in the comparator trial populations will help explain the results of the analysis. A sensitivity analysis should be presented additionally, as real-world outcomes may vary significantly from the clinical trial populations.

Figure 3: Cost-Effectiveness Space[4]



Adapted from: Value for money of drugs/medical devices. Crecon Medical Assessment, Inc. **www.crecon.co.jp/pharmaco_english.** Accessed December 11, 2015.

Table 1: MAIC Steps and Implications[7]	
MAIC Steps	**Example Implications**
Identify the appropriate trials to compare through a literature review	Trial A had lower response rates (80%) than Trial B (100%)
Identify differences in baseline characteristics	Trial A had sicker patients than Trial B
Adjust for baseline differences using individual patient-level data (IPLD) to match trial with only summary statistics	Sicker patients in Trial A don't "weigh" as much as less sick patients to adjust for baseline differences
Compare efficacy on a balanced population in a timely and reliable manner	After adjustments, Trial A response rates increase (90%) and Trial B response rates decrease (90%)

The CEA is an important analysis that allows payors to compare treatments in a way that incorporates efficacy (or effectiveness if real-world data is used), safety, and quality of life. It's important to understand clearly the underlying assumptions in a CEA before making conclusions on how it could impact the local population.

Comparative Effectiveness with Indirect Treatment Comparisons

In the absence of trials involving a direct comparison for treatments of interest, indirect treatment comparisons provide useful evidence of the difference in treatment effects.[5,6] An indirect treatment comparison (ITC) is one approach to compare particular treatments to each other, so long as there is a common comparator. ITCs can use the relative effects of the treatments of interest to the common comparator to provide information on expected differences between the two. At times, both direct comparisons and indirect comparisons are available, and utilizing information from both may be helpful to refine the exact estimate, called mixed treatment comparisons. Layering on top of this, if there are multiple randomized controlled trials (RCTs), including treatments compared directly or indirectly, this information can be synthesized in what is known as a network meta-analysis.[5,6]

In Figure 4 (comparing A, B, and C), treatment B has been compared to treatment A in one trial, treatment A compared to treatment C in another trial. Therefore, the indirect treatment comparison anchors the relative treatment effects of C versus A to B versus A to make a statement about B versus C.[5,6] This is an important concept because often randomized controlled trials or networks of RCTs are not available and the only data that we have is versus an older treatment. With data from ITCs, payors can evaluate the relative difference rather than just comparing trials side by side. Using ITCs prevents two pitfalls of comparing trials side by side (using only the treatment arm of interest): It helps to adjust for baseline disease differences and avoids the concept of "breaking randomization" (misinterpreting placebo effects).

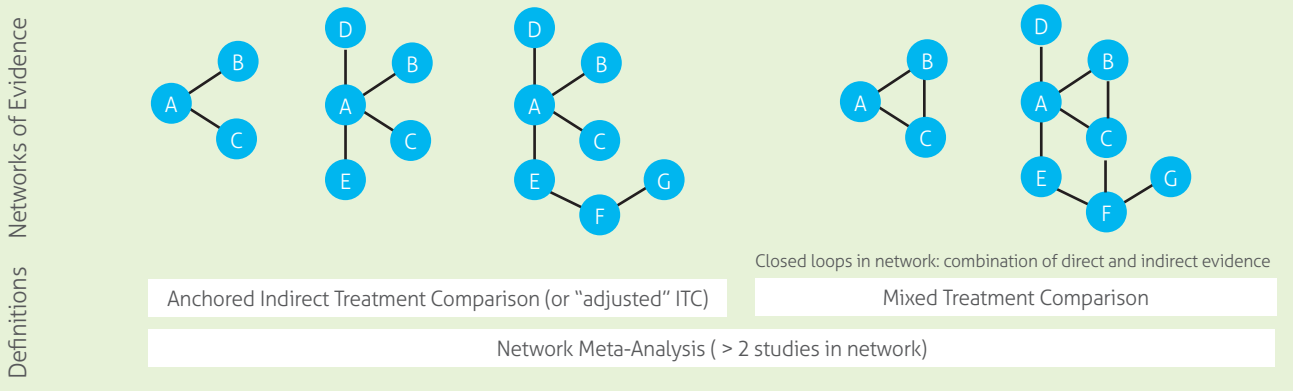
One novel approach that has been introduced to the literature recently is called a matching-adjusted indirect comparison (MAIC). When you compare trials, it is inherent that differences will exist in baseline characteristics or disease severity, leading to conflicting conclusions of comparative effectiveness.[7] Manufacturers that have access to individual patient-level data (IPLD) for one trial (but not necessarily all trials) can use this approach to adjust for differences in baseline characteristics. The plan should request MAIC or ITC data from the manufacturer when using multiple clinical trials and the data is not otherwise available. The MAIC approach follows the steps in Table 1.[7]

The MAIC approach is a new statistical method, and understanding this approach can help provide tools to make appropriate decisions when comparing treatments.

Importance of Real-World Research

Conducting both prospective and retrospective analysis within payor organizations or "real-world" research is a critical part of outcomes research. Clinical trials are important and can provide critical information on the efficacy and safety of drugs or interventions. However, effectiveness research or research that is done in routine clinical settings can provide information that health care providers and decision-makers can directly adopt. As payors have access to data on a large health plan population, this robust data can provide important information otherwise unattainable to inform decision-making. Comparative effectiveness research requires the development, expansion, and use of a variety of data sources and methods to conduct timely and relevant research and disseminate the results in a form that is quickly usable by clinicians, patients, policymakers, health plans, and other payors.

Figure 4: Indirect Treatment Comparisons and Meta-Analysis[5,6]



A number of steps are involved in conducting this research and in ensuring continued development of the research infrastructure to sustain and advance these efforts:[8]

1. Identify new and emerging clinical interventions
2. Review and synthesize current medical research
3. Identify gaps between existing medical research and the needs of clinical practice
4. Promote and generate new scientific evidence and analytic tools
5. Train and develop clinical researchers
6. Translate and disseminate research findings to diverse stakeholders

By understanding the level of clinical and research expertise available within the health plan network, researchers can be identified to collaborate and study the interventions of interest in a real-world setting, thereby providing meaningful data to aid in decision-making.

One of the goals of HEOR is to provide data on the relative clinical, economic, and humanistic value of treatments. A number of approaches have been developed to attempt to provide different snapshots of value. Depending on the stakeholder or payor, different types of analysis may provide impactful information. Understanding the concepts, purpose, and limitations behind each approach is important for health care decision-makers to evaluate new and existing treatment interventions.

REFERENCES

1. Holtorf AP, Brixner D, Bellows B, et al. Current and future use of HEOR data in healthcare decision-making in the United States and in emerging markets. *Am Health Drug Benefits.* 2012;5(7):428-438.
2. Sullivan S, Mauskopf JA, Augustovski F, et al. Budget impact analysis — Principles of good practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value in Health.* 2014;17(1):5-14.
3. *Health care cost, quality, and outcomes: ISPOR book of terms.* International Society for Pharmacoeconomics and Outcomes Research: Lawrenceville, NJ, USA, 2003.
4. Sher DJ, Punglia RS. Decision analysis and cost-effectiveness analysis for comparative effectiveness research — A primer. *Semin Radiat Oncol.* 2014;24(1):14-24.
5. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value in Health.* 2011;14(4):417-428.
6. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. *Value in Health.* 2011;14(4):429-437.
7. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: A new tool for timely comparative effectiveness research. *Value in Health.* 2012;15(6):940-947.
8. What is comparative effectiveness research. Agency for Healthcare Research and Quality website. **http://effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1.** Accessed December 11, 2015.

New Oncology Rating and Recommendation Systems

A Look at the National Comprehensive Cancer Network's Evidence Blocks and the American Society of Clinical Oncology's Value Framework

Cancer is a devastating disease with physical, mental, and financial implications on the lives of patients and their loved ones. In 2016, the American Cancer Society estimates that a total of 1,685,210 new cancer cases will be diagnosed, and 595,690 cancer deaths will occur.[1] In addition, national expenditures for cancer care in the United States reached approximately $125 billion in 2010 and may reach $156 billion by 2020.[2] Fortunately, the development of medications and treatment options to increase survival and quality of life continues.

With many drug regimens and treatment options available, guidelines to support physicians and patients in cancer management are essential. The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have each developed guidelines for assessing treatment for specific cancer types to assist with the evaluation and selection of cancer treatment regimens.

ASCO Value Framework

ASCO's focus, since it was founded in 1964, has evolved to include an emphasis on the value in patient care, with the creation of the Value in Cancer Care Task Force.[2,3] The Task Force targets three elements as the primary focus of its efforts, which include:

- Clinical benefit (efficacy)
- Toxicity (safety)
- Cost (efficiency)[3]

These three measures were selected due to their alignment with the Institute of Medicine's elements of quality health care delivery because they are readily measured, outcomes are obtained from high-quality medical evidence via clinical trials, and corresponds with the core mission of clinical oncologists.[3]

The Task Force developed a physician-guided tool, which it identifies as the "framework" to assist physicians and patients in making decisions regarding appropriate cancer care. Each framework includes information derived from randomized trials in peer-reviewed journals.[3,4] Two versions of the framework have been developed, one for advanced cancer and the other for potentially curative treatments, as seen in Table 1.[3-5]

The frameworks are based upon a point system, with points either added or subtracted in each category.[3] For advanced disease, the framework includes an assessment of six factors:

1. The physician must address clinical benefit using overall survival, progression-free survival, or response rate to determine a clinical benefit score.
2. The regimen's toxicity is assessed using a framework-based scale to rate whether the regimen chosen offers an improvement in toxicity over alternative treatments.[3]
3. Bonus points are awarded for a regimen's palliation of symptoms or if the regimen results in an improvement in a treatment-free interval.
4. The regimen's net health benefit — the sum of the clinical benefit score, toxicity score, and bonus points — is determined.
5. The regimen's cost is determined considering drug-acquisition cost and the treatment regimen cost per month, including consideration of patient's copay expenses.[3]
6. Final scores are tabulated and displayed in comparison of one regimen to another to support the making of an informed decision.

The framework for the curative treatment is similar in its step-by-step process. Clinical benefit is again calculated but is based on hazard ratio or disease-free survival, rather than upon the advanced disease criteria (overall survival, progression-free survival, or response rate).[3] The rest of the framework is the same — determining regimen toxicity, net health benefit, and regimen cost based on drug-acquisition cost and patient copay. As with the advanced disease framework, the values for the curative framework are calculated and displayed to provide a summary and comparison of the clinical benefit, toxicity, net health benefit, and cost of each therapeutic regimen assessed.[3,4]

When these framework proposals were released in 2015, ASCO sought comments from providers and patients.[3,4] Initially, four clinical scenarios were tested:

- First-line treatment of metastatic non-small cell lung cancer
- Treatment of advanced multiple myeloma
- Treatment of metastatic castration-resistant prostate cancer
- Adjuvant therapy for women with human epidermal growth factor receptor 2-positive breast cancer

In some clinical scenarios, the framework analysis demonstrated that a newer, more expensive regimen had a greater net health

benefit than the former standard of care.[3,4] In other scenarios, the opposite occurred and the newer regimen showed little to no net health benefit. ASCO stresses its proposed frameworks are intended to educate patients and help them to be confident in their care, not to limit their options based upon reported scores.[4]

NCCN Evidence Blocks

Similar to ASCO, the NCCN has made changes to its guidelines to support an individualized approach to patient care. At the NCCN 20th Annual Conference, a roundtable discussion addressed the optimal characteristics of a clinical practice guideline. Participants reflected on the growing complexity of guidelines and management of the uptake of new medications.[6-8] As a result of these conversations, NCCN Evidence Blocks were proposed as a means of addressing the need for personalized treatments and decision-making considering unique patient concerns.[7-9] In 2015 NCCN released its value-assessment initiative — the NCCN Evidence Blocks — as seen in Figure 1.[6,7,9]

The Evidence Blocks are currently available for chronic myeloid leukemia (CML) and multiple myeloma, as well as breast, colon, and kidney cancers, and offer a visual representation of treatment based on five attributes.[6,7] These attributes include:

- Efficacy of regimen/agent
- Safety of regimen/agent
- Quality of evidence
- Consistency of evidence
- Affordability of regimen/agent[9]

The blocks are displayed on a grid scale, with the attributes listed across the horizontal axis and ranked according to a 1 to 5 scale on the vertical axis.[9]

On this scale, a score of 1 indicates a result that is least favored, while 5 represents a quality most favored. The efficacy measure is assessed according to the extent that an intervention is helpful in prolonging life, arresting disease progression, or reducing symptoms of a medical condition, and ranges from a low score, palliative effect only (1), to highly effective (5).[9]

The second category, safety, is the assessment of the relative likelihood of side effects from an intervention, with fewer side effects being scored on a scale of highly toxic (1) to usually no meaningful toxicity (5).[9]

Quality and quantity of evidence refers to the number and types of clinical trials regarding a particular intervention, weighing depth of evidence, on a scale ranging from poor quality (1) to high quality (5).[9]

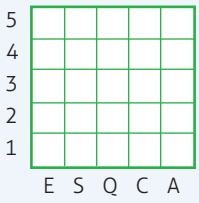
Consistency of evidence refers to the degree that the clinical trials addressing an intervention demonstrate consistent results, based on a scale ranging from anecdotal evidence only (1) to highly consistent (5).

Affordability refers to the overall cost of an intervention — including drug cost, required supportive care, infusions, toxicity monitoring, management of toxicity, probability of care being delivered in the hospital, etc. — with less expensive interventions being rated more highly than more expensive on a scale from very expensive (1) to very inexpensive (5).[9]

The efficacy and safety data included within the Evidence Blocks integrates input from panel members regarding published data

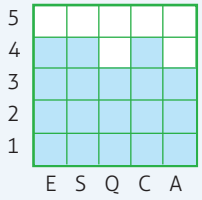
Figure 1: NCCN Evidence Blocks[9]

NCCN Evidence Blocks Categories and Definitions



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Table 1: Overview of the Frameworks[5]		
Measure	**Curative Framework**	**Advanced Cancer Framework**
Clinical Benefit (+80 possible points) How effective is the regimen according to the relevant metrics?	Relevant metrics: overall survival, disease-free progression	Relevant metrics: overall survival, disease-free progression, response rate
Toxicity (-20 to +20 points) Is the regimen substantially worse or better tolerated than the standard of care?	Relevant metric: Frequency of Grade 3-5 toxicities as defined by Common Terminology Criteria for Adverse Events	Relevant metric: Frequency of Grade 3-5 toxicities as defined by Common Terminology Criteria for Adverse Events
Bonus Points (+30 possible points)	No bonus-point option	Palliation bonus points if substantial improvement in cancer-related symptoms is reported in a randomized trial of treatment
Range of Possible Net Health Benefit Scores	-20 to 100	-20 to 130

along with their real-world clinical experience. NCCN intends to publish Evidence Blocks within systemic therapies applying to breast, colon, non-small cell lung, and rectal cancers.[9] The group has stated a goal of releasing Evidence Blocks for other systemic therapies for all NCCN guideline sections, potentially by the end of 2016.[9] The Evidence Blocks are intended to be designed so that a quick scan of the blocks for each therapy can be done and the appropriate intervention can be selected based on patient needs. The goal of these Evidence Blocks is to provide insight to support educated decision-making in selecting therapies.[9] The NCCN guidelines are intended to assist all individuals involved in the decision-making in cancer care, including physicians, nurses, pharmacists, payors, patients, and their families. The development of the NCCN guidelines is an ongoing and iterative process, based on a critical review of the best available evidence and the derivation of recommendations by a multidisciplinary panel of experts in the field of cancer.[9]

A Move Toward Value-Based Medicine

The ASCO and NCCN formats both attempt to bridge the gap between health care providers and patients, focusing on efficacy, safety, and cost. However, they vary from one another as well. The ASCO framework includes a form that the physician must complete to assess drugs being considered for inclusion in the patient's regimen. From here, the physician interprets the results of the framework to see how the numeric results correspond with patient needs.[3,9] NCCN's Evidence Blocks expand on factors influencing choices of care, including quality and consistency of evidence. Both guidelines can be used to support patient-centered cancer care treatment decisions that incorporate patient-specific considerations within the diseases for which the framework or Evidence Block assessment has been developed. Once the physician completes the ASCO framework, a comparison of therapies can be done to make a patient-specific value-based decision. Likewise, a quick evaluation of the NCCN blocks can provide a concise and evidence-based resource to support appropriate, patient-centered decisions.[3,9]

Through the use of these strategic tools for assessing and individualizing cancer treatment regimens, health care professionals and health plans may modify the manner in which treatment regimens are evaluated. The intent is to provide insight into the most cost-effective products that can be evaluated on a patient-specific basis. Additionally, payors may be able to utilize these tools to create coverage criteria that support the attainment of patient specific, physician, patient and health plan objectives — both clinical and economic. The true clinical and economic impact that these value assessments will have on patient management remains to be seen. However, the development of these two scoring systems is a positive step toward value-based medicine in oncology.

REFERENCES

1. Simon S. Cancer statistics report: Death rate down 23% in 21 years. American Cancer Society website. **www.cancer.org/cancer/news/news/cancer-statistics-report-death-rate-down-23-percent-in-21-years.** 2016. Accessed January 12, 2016.
2. ASCO profile and mission statement. American Society of Clinical Oncology website. **www.asco.org/about-asco/asco-profile-and-mission-statement.** Accessed January 13, 2016.
3. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol.* June 22, 2015.
4. ASCO publishes conceptual framework to assess the value of new cancer treatment options. American Society of Clinical Oncology. News release. June 22, 2015.
5. Hawes K. How ASCO scores the 'health benefit' of curative cancer drugs. The Advisory Board Company website. **www.advisory.com/research/oncology-roundtable/oncology-rounds/2015/09/asco-health-benefit-score.** September 28, 2015. Accessed January 13, 2016.
6. What is NCCN? National Comprehensive Cancer Network website. **www.nccn.org/patients/about/what.aspx.** Accessed January 13, 2016.
7. Final roundtable of the NCCN 20th Annual Conference explores essential characteristics of clinical practice recommendations. National Comprehensive Cancer Network website. **www.nccn.org/about/news/newsinfo.aspx?NewsID=505.** Accessed January 13, 2016.
8. NCCN unveils Evidence Blocks for CML and multiple myeloma. National Comprehensive Cancer Network website. **www.nccn.org/about/news/newsinfo.aspx?NewsID=546.** Accessed January 13, 2016.
9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™. National Comprehensive Cancer Network website. **www.nccn.org/evidenceblocks.** Accessed January 13, 2016.

PIPELINE TRENDS

PRODUCT PIPELINE				
Drug	Manufacturer	PDUFA Date	Application Type	Expected Indication
Nuplazid™ (pimavanserin)	Acadia Pharmaceuticals Inc.	May 1, 2016	NDA	Parkinson's disease psychosis
Evomela™ (melphalan hydrochloride)	Spectrum Pharmaceuticals	May 9, 2016	NDA	Conditioning treatment prior to hematopoietic stem cell transplant (HSCT) for patients with multiple myeloma Palliative treatment of multiple myeloma
ZS-9 (sodium zirconium cyclosilicate)	ZS Pharma Inc.	May 26, 2016	NDA	Treatment of hyperkalemia
Eteplirsen	Sarepta Therapeutics	May 26, 2016	NDA	Duchenne muscular dystrophy
Probuphine® (buprenorphine hydrochloride)	Titan Pharmaceuticals	May 27, 2016	NDA	Long-term maintenance treatment of opioid addiction
Fanapt® (iloperidone)	Vanda Pharmaceuticals, Inc.	May 27, 2016	sNDA	Maintenance treatment of schizophrenia in adults
Obeticholic acid	Intercept Pharmaceuticals Inc.	May 29, 2016	NDA	Primary biliary cirrhosis
KP201/APAP (benzhydrocodone hydrochloride and acetaminophen)	KemPharm, Inc.	June 9, 2016	NDA	Short-term management of acute pain
Cabozantinib	Exelixis, Inc.	June 22, 2016	NDA	Second-line treatment of advanced renal cell carcinoma
Rociletinib	Clovis Oncology, Inc.	June 28, 2016	NDA	Mutant EGFR T790M-positive lung cancer
LPCN 1021	Lipocine, Inc.	June 28, 2016	NDA	Treat symptoms of low testosterone in hypogonadal men
SOF/VEL (sofosbuvir and velpatasvir)	Gilead Sciences, Inc.	June 28, 2016	NDA	Treatment of chronic genotype 1-6 hepatitis C virus infection
Repatha™ (evolocumab)	Amgen	July 10, 2016	sBLA	Monthly administration single-dosing option for treatment of adults with heterozygous familial hypercholesterolemia or clinical ASCVD
Aggrastat® (tirofiban HCl)	Medicure, Inc.	July 10, 2016	sNDA	Treatment of patients presenting with STEMI intended for PCI
Vesneo™ (latanoprostene bunod 0.024%)	Valeant Pharmaceuticals	July 21, 2016	NDA	Open angle glaucoma and ocular hypertension
Lifitegrast	Shire PLC	July 22, 2016	NDA	Treatment of signs and symptoms of dry eye disease
Bezlotoxumab	Merck	July 23, 2016	BLA	Prevention of *C. diff* infection reoccurrence
Dextenza™ (dexamethasone intracanalicular depot)	Ocular Therapeutix, Inc.	July 24, 2016	NDA	Post-operative ocular pain

PROJECTED UPCOMING LOEs			
Drug	Brand Manufacturer	Projected LOE Date	Day 1 Entrants
Crestor® (rosuvastatin calcium)	AstraZeneca	May 2, 2016	1
Cubicin® (daptomycin)	Merck	June 15, 2016	2
Prolensa™ (bromfenac sodium)	Bausch & Lomb	June 19, 2016	1
Nuvigil® (armodafinil)	Cephalon, Inc.	June 2016	1
Asacol® HD (mesalamine)	Actavis Pharma, Inc.	July 1, 2016	1
Zegerid® (omeprazole and sodium bicarbonate)	Salix Pharmaceuticals, Inc.	July 15, 2016	1
Ziana® (clindamycin phosphate and tretinoin)	Valeant Pharmaceuticals	July 2016	1

For Your Patients With IBS-D

Does the Threat of Diarrhea and Abdominal Pain Keep Looming?

VIBERZI targets the core components of IBS-D, diarrhea and abdominal pain, helping provide lasting relief*

*VIBERZI was studied in two placebo-controlled, Phase 3 trials in >2400 IBS-D adult patients (aged 18-80). A responder was defined as a patient with ≥30% reduction in abdominal pain AND improvement in stool consistency to <5 on the Bristol Stool Scale on at least 50% of days throughout 12 and 26 weeks. Improvement in abdominal pain in the absence of a bowel movement was also considered a response day. The proportion of patients who were combined responders to VIBERZI at each 4-week interval was numerically higher than placebo as early as month 1 through month 6.

Indication

VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

Important Safety Information

Contraindications

- Known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction; a history of pancreatitis; structural diseases of the pancreas.
- Alcoholism, alcohol abuse, alcohol addiction, or drink more than 3 alcoholic beverages per day.
- Severe hepatic impairment.
- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Sphincter of Oddi Spasm:

- There is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (eg, biliary-type pain) with VIBERZI. These events were reported in less than 1% of patients receiving VIBERZI in clinical trials.
- Patients without a gallbladder are at increased risk. Consider alternative therapies before using VIBERZI in patients without a gallbladder and evaluate the benefits and risks of VIBERZI in these patients.

Please see additional Important Safety Information and brief summary of full Prescribing Information on following pages.

Viberzi™
(eluxadoline) tablets C IV
75 mg • 100 mg

Be Proactive Against IBS-D

VIBERZI: Lasting Relief of Diarrhea and Abdominal Pain*

VIBERZI binds to opioid receptors in the gut, which may play a key role in controlling GI motility and visceral hypersensitivity

- Based on nonclinical data

VIBERZI provides sustained efficacy against diarrhea and abdominal pain

- The proportion of patients who were combined responders to VIBERZI at each 4-week interval was numerically higher than placebo as early as month 1 through month 6*

VIBERZI has a well-established safety profile from trials lasting up to 1 year

*A responder was defined as a patient with ≥30% reduction in abdominal pain AND improvement in stool consistency to <5 on the Bristol Stool Scale on at least 50% of days throughout 12 and 26 weeks. Improvement in abdominal pain in the absence of a bowel movement was also considered a response day.

Important Safety Information

Warnings and Precautions (continued)

Sphincter of Oddi Spasm (continued):

- Inform patients without a gallbladder that they may be at increased risk for symptoms of sphincter of Oddi spasm, such as elevated liver transaminases associated with abdominal pain or pancreatitis, especially during the first few weeks of treatment. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms of sphincter of Oddi spasm.

Pancreatitis:

- There is a potential for increased risk of pancreatitis not associated with sphincter of Oddi spasm; such events were reported in less than 1% of patients receiving VIBERZI in clinical trials, and the majority were associated with excessive alcohol intake. All pancreatic events resolved upon discontinuation of VIBERZI.
- Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting, associated with elevations of pancreatic enzymes. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of pancreatitis.

Adverse Reactions

- The most commonly reported adverse reactions (incidence >5% and greater than placebo) were constipation, nausea, and abdominal pain.

Please see brief summary of full Prescribing Information on following page.

Visit ViberziHCP.com to learn more

Viberzi™
(eluxadoline) tablets C IV
75 mg • 100 mg

Be Proactive Against IBS-D

Allergan

VIBERZI (eluxadoline) tablets, for oral use, CIV
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2015

INDICATIONS AND USAGE: VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

CONTRAINDICATIONS: VIBERZI is contraindicated in patients with: Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm *[see Warnings and Precautions]*; Alcoholism, alcohol abuse or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions]*; A history of pancreatitis; or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions]*; Severe hepatic impairment (Child-Pugh Class C). These patients are at risk for significantly increased plasma concentrations of eluxadoline *[see Use in Specific Populations]*; A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.

WARNINGS AND PRECAUTIONS: Sphincter of Oddi Spasm - Given the mu-opioid receptor agonism of VIBERZI, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (e.g., biliary-type pain) with VIBERZI. In clinical trials, sphincter of Oddi spasm occurred in less than 1% of patients receiving VIBERZI. The majority of these patients presented within the first week of treatment and the event resolved on discontinuation of VIBERZI. Patients without a gallbladder are at increased risk *[see Adverse Reactions]*. Consider alternative therapies before using VIBERZI in patients without a gallbladder and evaluate the benefits and risks of VIBERZI in these patients in the context of their symptom severity. The recommended dosage of VIBERZI is 75 mg twice daily in patients without a gallbladder *[see Dosage and Administration in full Prescribing Information]*. If VIBERZI is used in such a patient, inform them that they may be at increased risk for adverse reactions and monitor them for symptoms of sphincter of Oddi spasm, such as elevated liver transaminases associated with abdominal pain or pancreatitis, especially during the first few weeks of treatment. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain, (e.g., acute epigastric or biliary [i.e., right upper quadrant] pain), that may radiate to the back or shoulder with or without nausea and vomiting, associated with elevations of pancreatic enzymes or liver transaminases. Do not restart VIBERZI in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking VIBERZI *[see Contraindications]*. **Pancreatitis -** There is a potential for increased risk of pancreatitis, not associated with sphincter of Oddi spasm, when taking VIBERZI. Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in less than 1% of patients receiving VIBERZI in clinical trials. The majority were associated with excessive alcohol intake. All pancreatic events, whether or not associated with sphincter of Oddi spasm, resolved upon discontinuation of VIBERZI; patients did not have organ failure or local or systemic complications *[see Adverse Reactions]*. Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of pancreatitis such as acute abdominal or epigastric pain radiating to the back associated with elevations of pancreatic enzymes *[see Contraindications]*.

ADVERSE REACTIONS: The following adverse reactions described below and elsewhere in the labeling include: Sphincter of Oddi Spasm *[see Warnings and Precautions]*; Pancreatitis *[see Warnings and Precautions]*. **Clinical Trials Experience -** Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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. Over 1700 patients with IBS-D have been treated with 75 or 100 mg of VIBERZI twice daily in controlled trials. Exposures from placebo-controlled clinical trials in adult patients with IBS-D included 1391 exposed for 3 months, 1001 exposed for 6 months and 488 exposed for one year. Demographic characteristics were comparable between the treatment groups *[see Clinical Studies in full Prescribing Information]*. Data described below represent pooled data compared to placebo across the randomized trials. *Sphincter of Oddi Spasm* - In clinical trials, sphincter of Oddi spasm occurred in 0.2% (2/807) of patients receiving 75 mg and 0.8% (8/1032) of patients receiving 100 mg VIBERZI twice daily. Among patients receiving 75 mg, 1/807 (0.1%) patient experienced a sphincter of Oddi spasm presenting with abdominal pain but with lipase elevation less than 3 times the upper limit of normal (ULN) and 1/ 807 (0.1%) patient experienced a sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain; Among patients receiving 100 mg, 1/1032 (0.1%) patient experienced a sphincter of Oddi spasm manifested as pancreatitis and 7/1032 (0.7%) patients experienced sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain. In patients without a gallbladder, 2/165 (1.2%) and 8/184 (4.3%) of patients receiving 75 mg and 100 mg, respectively, experienced a sphincter of Oddi spasm vs 0/1317 (0%) in patients with a gallbladder who had received either 75 mg or 100 mg treatment. Of those patients who experienced a sphincter of Oddi spasm, 80% (8/10) reported their first onset of symptoms within the first week of treatment. The case of sphincter of Oddi spasm-induced pancreatitis occurred within minutes of taking the first dose of VIBERZI. No cases of sphincter of Oddi spasm occurred greater than 1 month after treatment onset. All events resolved upon discontinuation of VIBERZI, with symptoms typically improved by the following day. *Pancreatitis* - Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in 2/807 (0.2%) of patients receiving 75 mg and 3/1032 (0.3%) of patients receiving 100 mg VIBERZI twice daily in clinical trials. Of these 5 cases, 3 were associated with excessive alcohol intake, one was associated with biliary sludge, and in one case the patient discontinued VIBERZI 2 weeks prior to the onset of symptoms. All pancreatic events resolved with lipase normalization upon discontinuation of VIBERZI, with 80% (4/5) resolving within 1 week of treatment discontinuation. The case of sphincter of Oddi spasm-induced pancreatitis resolved within 24 hours of discontinuation. *Common Adverse Reactions* - **Table 1** provides the incidence of common* adverse reactions reported in > 2% of IBS-D patients in either VIBERZI treatment group and at an incidence greater than in the placebo group. Values are shown in parentheses as VIBERZI 100 mg twice daily (N=1032), VIBERZI 75 mg twice daily (N=807), and Placebo (N=975). Constipation (8, 7, 2); Nausea (7, 8, 5); Abdominal Pain** (7, 6, 4); Upper Respiratory Tract Infection (5, 3, 4); Vomiting (4, 4, 1); Nasopharyngitis (3, 4, 3); Abdominal Distention (3, 3, 2); Bronchitis (3, 3, 2); Dizziness (3, 3, 2); Flatulence (3, 3, 2); Rash*** (3, 3, 2); Increased ALT (3, 2, 1); Fatigue (2, 3, 2); Viral gastroenteritis (1, 3, 2).
* Reported in > 2% of VIBERZI-treated patients at either dose and at an incidence greater than in placebo-treated patients ** "Abdominal Pain" term includes: abdominal pain, abdominal pain lower, and abdominal pain upper *** "Rash" term includes: dermatitis, dermatitis allergic, rash, rash erythematous, rash generalized, rash maculo-papular, rash papular, rash pruritic, urticaria, and idiopathic urticaria. Constipation was the most commonly reported adverse reaction in VIBERZI-treated patients in these trials. Approximately 50% of constipation events occurred within the first 2 weeks of treatment while the majority occurred within the first 3 months of therapy. Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg VIBERZI. Similar rates of constipation occurred between the active and placebo arms beyond 3 months of treatment. *Adverse Reactions Leading to Discontinuation* - Eight percent of patients treated with 75 mg, 8% of patients treated with 100 mg VIBERZI and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the VIBERZI treatment groups, the most common reasons for discontinuation due to adverse reactions were constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg). In comparison, less than 1% of patients in the placebo group withdrew due to constipation or abdominal pain. *Less Common Adverse Reactions* - Adverse reactions that were reported in ≤ 2% of VIBERZI-treated patients are listed below by body system. Gastrointestinal: gastroesophageal reflux disease; General disorders and administration site conditions: feeling drunk; Investigations: increased AST; Nervous system: sedation, somnolence; Psychiatric disorders: euphoric mood; Respiratory: asthma, bronchospasm, respiratory failure, wheezing.

DRUG INTERACTIONS: The metabolism of eluxadoline by CYP pathways has not been clearly established. In addition, the potential of eluxadoline to inhibit CYP3A4 in the gut has not been established. **Tables 2** and **3** include drugs which demonstrated a clinically important drug interaction with VIBERZI or which potentially may result in clinically relevant interactions. **Table 2: Established and Other Potentially Clinically Relevant Interactions Affecting VIBERZI: OATP1B1 Inhibitors -** *Clinical Impact:* Increased exposure to eluxadoline when coadministered with cyclosporine *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Administer VIBERZI at a dose of 75 mg twice daily *[see Dosage and Administration in full Prescribing Information]* and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]. Examples:* cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag. **Strong CYP Inhibitors* -** *Clinical Impact:* Potential for increased exposure to eluxadoline *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]. Examples:* ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6). **Drugs that Cause Constipation -** *Clinical Impact:* Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions. *Intervention:* Avoid use with other drugs that may cause constipation (see below); loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs. *Examples:* alosetron, anticholinergics, opioids.* As a precautionary measure due to incomplete information on the metabolism of eluxadoline. **Table 3: Established and Other Potentially Clinically Relevant Interactions Affecting Drugs Co-Administered with VIBERZI: OATP1B1 and BCRP Substrate -** *Clinical Impact:* VIBERZI may increase the exposure of co-administered OATP1B1 and BCRP substrates. Increased exposure to rosuvastatin when co-administered with VIBERZI with a potential for increased risk of myopathy/rhabdomyolysis *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Use the lowest effective dose of rosuvastatin (see prescribing information of rosuvastatin for additional information on recommended dosing). **CYP3A Substrates with Narrow Therapeutic Index -** *Clinical Impact:* Potential for increased exposure of co-administered drug *[see Clinical Pharmacology in full Prescribing Information]. Intervention:* Monitor drug concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued. *Examples:* alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.

USE IN SPECIFIC POPULATIONS: Pregnancy - *Risk Summary:* There are no studies with VIBERZI in pregnant women that inform any drug-associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. In animal reproduction studies, oral and subcutaneous administration of eluxadoline to rats and rabbits during organogenesis at doses approximately 51 and 115 times the human exposure after a single oral dose of 100 mg, respectively, demonstrated no teratogenic effects. In a pre- and postnatal development study in rats, no adverse effects were observed in offspring with oral administration of eluxadoline at doses approximately 10 times the human exposure *[see Data]. Data* - Animal Data: Eluxadoline administered as combined oral (1000 mg/kg/day) and subcutaneous (5 mg/kg/day) doses during the period of organogenesis to rats and rabbits (exposures about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (with exposures about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In the same study, eluxadoline was detected in the milk of lactating rats administered oral doses of 100, 300 and 1000 mg/kg/day (with exposures about 1.8, 3 and 10 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Milk samples were collected from six lactating females per group on lactation day 12. Mean concentrations of eluxadoline in the milk of lactating rats on lactation day 12 were 2.78, 5.49 and 44.02 ng/mL at 100, 300 and 1000 mg/kg/day, respectively. **Lactation -** *Risk Summary:* No data are available regarding the presence of eluxadoline in human milk, the effects of eluxadoline on the breastfed infant, or the effects of eluxadoline on milk production. However, eluxadoline is present in rat milk *[see Use in Specific Populations]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIBERZI and any potential adverse effects on the breastfed infant from VIBERZI or from the underlying maternal condition. **Pediatric Use -** Safety and effectiveness in pediatric patients have not been established. *Juvenile Toxicology Data:* Eluxadoline was orally administered to juvenile rats at 500, 750, and 1500 mg/kg/day (about 16, 54 and 30 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) for 4 weeks. There were no adverse physiologic effects related to eluxadoline. Based on these results, the NOAEL for male and female juvenile rats was 1500 mg/kg/day (about 30 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). **Geriatric Use -** Of 1795 IBS-D patients in clinical trials of VIBERZI who received 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old. No overall differences in effectiveness were observed between these patients and younger patients. There were no overall differences in the types of adverse reactions observed between elderly and younger patients; however, a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs 59%), serious adverse reactions (9% vs 4%), and gastrointestinal adverse reactions (39% vs 28%). **Hepatic Impairment -** Plasma concentrations of eluxadoline increase in patients with hepatic impairment *[see Clinical Pharmacology in full Prescribing Information]*. VIBERZI is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) as plasma concentrations of eluxadoline increase significantly (16-fold) and there is no information to support the safety of VIBERZI in these patients. In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, plasma concentrations of eluxadoline increase to a lesser extent (6- and 4-fold, respectively). Administer VIBERZI at a reduced dose of 75 mg twice daily to these patients *[see Dosage and Administration in full Prescribing Information]*. Monitor patients with any degree of hepatic impairment for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions]*.

DRUG ABUSE AND DEPENDENCE: Controlled Substance - VIBERZI is listed in Schedule IV of the Controlled Substances Act. **Abuse -** In a drug discrimination study in monkeys, intravenous administration of eluxadoline hydrochloride produced full generalization to the morphine cue. In a self-administration study in monkeys, eluxadoline hydrochloride was self-administered to a degree that was less than that of heroin but greater than that of saline. Adverse reactions of euphoria and feeling drunk were reported in clinical trials of IBS-D evaluating 75 mg and 100 mg doses of VIBERZI. The rate of euphoria was 0% for 75 mg and 0.2% (2/1032) for 100 mg and the rate of feeling drunk was 0.1% (1/807) for 75 mg and 0.1% (1/1032) for 100 mg. In contrast, in two human abuse potential studies conducted in recreational opioid-experienced individuals, supratherapeutic oral doses of VIBERZI (300 mg and/or 1000 mg) and intranasal doses of VIBERZI (100 mg and/or 200 mg) produced the adverse reaction of euphoria (at a rate ranging from 14% to 28%) that was greater than that of placebo (0% to 5%) but less than that of oxycodone (44% to 76%). In the two human abuse potential studies, supratherapeutic oral and intranasal doses of VIBERZI produced small but significant increases in positive subjective measures such as Drug Liking and High compared to placebo. Supratherapeutic oral and intranasal doses of VIBERZI also produced small but significant increases in negative subjective measures such as Drug Disliking and Dysphoria compared to placebo. In the same studies, oxycodone (30 mg and 60 mg oral, and 15 and 30 mg intranasal) produced significantly greater responses on positive and negative subjective measures than those produced by eluxadoline and placebo. **Dependence -** In studies with monkeys and rats in which eluxadoline and eluxadoline hydrochloride were chronically administered, discontinuation of the drug did not lead to behavioral signs of withdrawal, a measure of physical dependence. However, the ability of eluxadoline hydrochloride in monkeys to induce self-administration suggests that the drug is sufficiently rewarding to produce reinforcement. In two human abuse potential studies with VIBERZI conducted in recreational opioid-experienced individuals, euphoria was reported at a rate of 14% to 28%. These data suggest that eluxadoline may produce psychological dependence.

OVERDOSAGE: No reports of overdosage with VIBERZI have been reported. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. The patient should be carefully observed and given standard supportive treatment as required. Given eluxadoline's action at opioid receptors, administration of a narcotic mu-opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, subjects should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection.

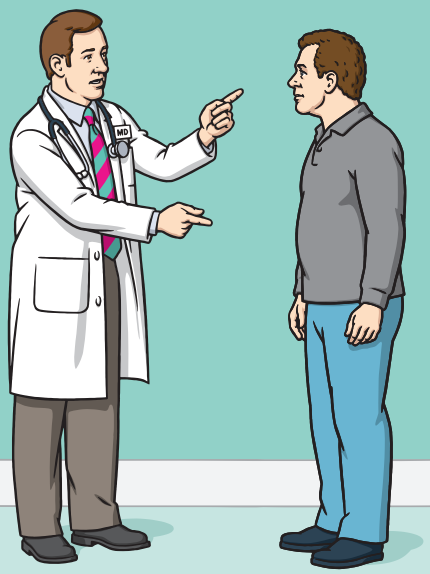
Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: June 2015 ELX32306 - A - 05/15

Please also see full Prescribing Information at www.VIBERZI.com.

IN ADULT PATIENTS WITH CHRONIC NON-CANCER PAIN

HOW DO YOU TREAT OPIOID-INDUCED CONSTIPATION?



"There's some good Mu's and some not-so-good Mu's."

Opioids work by binding to mu-receptors in the brain and other parts of the central nervous system to block pain signals.[1] But they also bind to mu-receptors in the bowel, which can cause opioid-induced constipation (OIC).[1] MOVANTIK™ (naloxegol) is the first oral therapy in its class indicated for the treatment of OIC in adult patients with chronic non-cancer pain.

VISIT **TRYMOVANTIK.COM** AND ORDER FREE SAMPLES FOR YOUR APPROPRIATE PATIENTS

IMPORTANT SAFETY INFORMATION ABOUT MOVANTIK

- MOVANTIK™ (naloxegol) is contraindicated in:
  - — Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation
  - — Patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms
  - — Patients with a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients
- Cases of GI perforation have been reported with the use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if this symptom develops
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning, occurred in patients treated with MOVANTIK. Patients receiving methadone as therapy for their pain condition were observed in the clinical trials to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids. Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. These patients (eg, multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy) were not enrolled in the clinical studies. Take into account the overall risk-benefit profile when using MOVANTIK in such patients. Monitor for symptoms of opioid withdrawal when using MOVANTIK in such patients
- The most common adverse reactions with MOVANTIK as compared to placebo in clinical trials were: abdominal pain (21% vs 7%), diarrhea (9% vs 5%), nausea (8% vs 5%), flatulence (6% vs 3%), vomiting (5% vs 4%), headache (4% vs 3%), and hyperhidrosis (3% vs <1%)

Please see the Brief Summary of full Prescribing Information on the adjacent pages.

Reference: 1. Brock C et al. *Drugs.* 2012;72:1847-1865.

Daiichi-Sankyo AstraZeneca

movantik™ (naloxegol) 25 mg tablets

It Starts With 'Mu'

MOVANTIK™ (naloxegol) tablets, for oral use

BRIEF SUMMARY of PRESCRIBING INFORMATION

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

MOVANTIK (naloxegol) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

DOSAGE AND ADMINISTRATION

Administration

- Discontinue all maintenance laxative therapy prior to initiation of MOVANTIK. Laxative(s) can be used as needed if there is a suboptimal response to MOVANTIK after three days.
- Alteration in analgesic dosing regimen prior to initiating MOVANTIK is not required.
- MOVANTIK has been shown to be efficacious in patients who have taken opioids for at least 4 weeks. Sustained exposure to opioids prior to starting MOVANTIK may increase the patient's sensitivity to the effects of MOVANTIK *[see Clinical Studies (14) in Full Prescribing Information]*.
- Take MOVANTIK on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal.
- Swallow tablets whole, do not crush or chew.
- Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK.
- Discontinue MOVANTIK if treatment with the opioid pain medication is also discontinued.

Adult Dosage

The recommended MOVANTIK dosage is 25 mg once daily in the morning.

If patients are not able to tolerate MOVANTIK, reduce the dosage to 12.5 mg once daily *[see Clinical Pharmacology (12.2) in Full Prescribing Information]*.

Dosage in Adult Patients with Renal Impairment

The starting dosage for patients with creatinine clearance (CLcr) < 60 mL/min (i.e., patients with moderate, severe or end-stage renal impairment) is 12.5 mg once daily. If this dosage is well tolerated but OIC symptoms continue, the dosage may be increased to 25 mg once daily taking into consideration the potential for markedly increased exposures in some patients with renal impairment and the increased risk of adverse reactions with higher exposures *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Dosage Recommendations due to Drug Interactions

Avoid concomitant use of MOVANTIK with moderate CYP3A4 inhibitor drugs (e.g., diltiazem, erythromycin, verapamil). If concurrent use is unavoidable, reduce the MOVANTIK dosage to 12.5 mg once daily and monitor for adverse reactions *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

DOSAGE FORMS AND STRENGTHS

MOVANTIK (naloxegol) is available in two strengths:

- Tablets: 12.5 mg supplied as mauve, oval, biconvex, film-coated, intagliated with "nGL" on one side and "12.5" on the other side.
- Tablets: 25 mg supplied as mauve, oval, biconvex, film-coated, intagliated with "nGL" on one side and "25" on the other side.

CONTRAINDICATIONS

MOVANTIK is contraindicated in:

- Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation *[see Warnings and Precautions (5.1) in Full Prescribing Information]*.
- Patients concomitantly using strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning *[see Drug Interactions (7.1) and Pharmacokinetics (12.3) in Full Prescribing Information]*.
- Patients who have had a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients.

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using MOVANTIK in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent or worsening abdominal pain; discontinue MOVANTIK in patients who develop this symptom *[see Contraindications (4) in Full Prescribing Information]*.

Opioid Withdrawal

Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning have occurred in patients treated with MOVANTIK *[see Adverse Reactions (6.1) in Full Prescribing Information]*. In addition, patients receiving methadone as therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids *[see Adverse Reactions (6.1)]*. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using MOVANTIK in such patients. Monitor for symptoms of opioid withdrawal in such patients.

ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in labeling include:

- Gastrointestinal perforation *[see Warnings and Precautions (5.1) in Full Prescribing Information]*
- Opioid withdrawal *[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 MOVANTIK in 1497 patients in clinical trials, including 537 patients exposed for greater than six months, and 320 patients exposed for 12 months.

The safety data described in Table 1 are derived from two double-blind, placebo-controlled trials (Studies 1 and 2) in patients with OIC and non-cancer related pain *[see Clinical Studies (14) in Full Prescribing Information]*.

Study 3 (n=302) was a safety extension study that allowed patients from Study 1 to continue the same blinded treatment for an additional 12 weeks. Safety data for patients in Study 3 are similar to those listed in Table 1.

Study 4 (n=844) was a Phase 3, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of naloxegol versus usual care treatment for OIC (as determined by the investigator and excluding peripheral opioid antagonists) in patients with non-cancer related pain. The population enrolled in Study 4 was similar to that of the other studies. Eligible patients were randomized in a 2:1 ratio to receive either naloxegol 25 mg once daily or usual care treatment for OIC. The most commonly used laxatives in the usual care group were rectal stimulants (e.g., bisacodyl), oral stimulants (e.g., senna), and oral osmotics (e.g., macrogol, magnesium). Safety data for patients in Study 4 are similar to those listed in Table 1.

Table 1 lists adverse reactions in pooled Studies 1 and 2 occurring in ≥ 3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

Table 1. Adverse Reactions* in Patients with OIC and Non-Cancer Pain (Studies 1 and 2)

Adverse Reaction	MOVANTIK 25 mg (n=446)	MOVANTIK 12.5 mg (n=441)	Placebo (n=444)
Abdominal Pain	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%
Vomiting	5%	3%	4%
Headache	4%	4%	3%
Hyperhidrosis	3%	<1%	<1%

*Adverse reactions occurring in ≥ 3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

Opioid Withdrawal

Possible opioid withdrawal, defined as at least three adverse reactions potentially related to opioid withdrawal that occurred on the same day and were not all related to the gastrointestinal system, occurred in less than 1% (1/444) of placebo subjects, 1% (5/441) receiving MOVANTIK 12.5 mg, and 3% (14/446) receiving MOVANTIK 25 mg in Studies 1 and 2 regardless of maintenance opioid treatment. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Patients receiving methadone as therapy for their pain condition were observed in Studies 1 and 2 to have a higher frequency of gastrointestinal adverse reactions than patients receiving other opioids [39% (7/18) vs. 26% (110/423) in the 12.5 mg group; 75% (24/32) vs. 34% (142/414) in the 25 mg group].

DRUG INTERACTIONS

Effects of Other Drugs on MOVANTIK

Table 2 displays the effects of other drugs on MOVANTIK.

Table 2. Effects of Other Drugs on MOVANTIK

Concomitant Agent	Mechanism of Action	Clinical Recommendation
CYP3A4 Inhibitors		
• Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)	• Increase plasma naloxegol concentrations and may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.	• Use with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4)]*.
• Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil)		• Avoid use with moderate CYP3A4 inhibitors; if unavoidable, decrease the dosage of MOVANTIK to 12.5 mg once daily and monitor for adverse reactions *[see Dosage and Administration (2.4)]*.
• Weak CYP3A4 inhibitors (e.g., quinidine, cimetidine)	• Clinically significant increases in naloxegol concentrations are not expected.	• No dosage adjustments are necessary.
• Grapefruit or grapefruit juice*	• Can increase plasma naloxegol concentrations.	• Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK *[see Dosage and Administration (2.1)]*.
CYP3A4 Inducers		
• Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort)	• Significantly decrease plasma naloxegol concentrations and may decrease the efficacy of MOVANTIK *[see Clinical Pharmacology (12.3)]*.	• Use with strong CYP3A4 inducers is not recommended.
Other Drug Interactions		
• Other opioid antagonists	• Potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal.	• Avoid use of MOVANTIK with another opioid antagonist.

*The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength)

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with MOVANTIK in pregnant women. The use of MOVANTIK during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC (area under the plasma concentration-time curve) at the maximum recommended human dose. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rabbits during the period of organogenesis at doses up to 409 times the human AUC at the maximum recommended human dose. MOVANTIK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Oral administration of up to 750 mg/kg/day naloxegol in rats (1452 times the human AUC at the maximum recommended human dose) and 450 mg/kg/day naloxegol in rabbits (409 times the human AUC at the maximum recommended human dose) during the period of organogenesis produced no adverse effects on embryo-fetal development. Oral administration of up to 500 mg/kg/day in rats (195 times the maximum recommended human dose based on body surface area) during the period of organogenesis through lactation produced no adverse effects on parturition or the offspring.

Nursing Mothers

It is unknown whether MOVANTIK is present in human milk; however, naloxegol is present in rat milk and is absorbed in nursing rat pups. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in clinical studies of MOVANTIK, 11 percent were 65 and over, while 2 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

MOVANTIK exposure was higher in elderly healthy Japanese subjects compared to young subjects *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. No dosage adjustment is needed in elderly patients.

Renal Impairment

Some subjects with creatinine clearance (CLcr) values < 60 mL/minute (i.e., moderate, severe or end-stage renal disease) were shown to exhibit markedly higher systemic exposure of naloxegol compared to subjects with normal renal function. The reason for these high exposures is not understood. However, as the risk of adverse reactions increases with systemic exposure, a lower starting dosage of 12.5 mg once daily is recommended. No dosage adjustment is needed in patients with mild renal impairment *[see Dosage and Administration (2.3), and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Hepatic Impairment

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol has not been evaluated. Avoid use of MOVANTIK in patients with severe hepatic impairment, as the dosage in these patients has not been determined. No dosage adjustment is required for patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In a clinical study of patients with OIC a daily dose of 50 mg (twice the recommended dosage), administered over 4 weeks, was associated with an increased incidence of GI adverse reactions, such as abdominal pain, diarrhea and nausea. These adverse reactions frequently occurred within 1-2 days after dosing.

No antidote is known for naloxegol. Dialysis was noted to be ineffective as a means of elimination in a clinical study in patients with renal failure.

If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

3097305 2/15 Revised 01/2015

Magellan Rx MANAGEMENT℠

CREATING SOLUTIONS

FOR COMPLEX PHARMACY CHALLENGES

At Magellan Rx Management, we deliver proven medical pharmacy management programs with real cost savings for this expensive and rapidly growing portion of specialty drug spend. We believe in leveraging our industry-leading oncology expertise to move beyond the traditional volume-focused market to deliver true value-driven solutions that drive down costs and improve patient health.

A trusted partner in leveraging advanced technology for increased efficiency and administrative ease

Evidence-based clinical programs and analytics drive better decision making for cost effective, value-driven outcomes

Supported by our clinical expertise of national oncology experts and key opinion leaders

Improving quality of care for our patients through education, outreach, and assistance programs

LET'S CONNECT TODAY!

800-659-4112
www.magellanrx.com