Magellan Rx Report Fall 2015

Fall 2015

A Comprehensive Approach to Treating Opioid Dependency

Evaluating the Clinical and Economic Success of ACOs

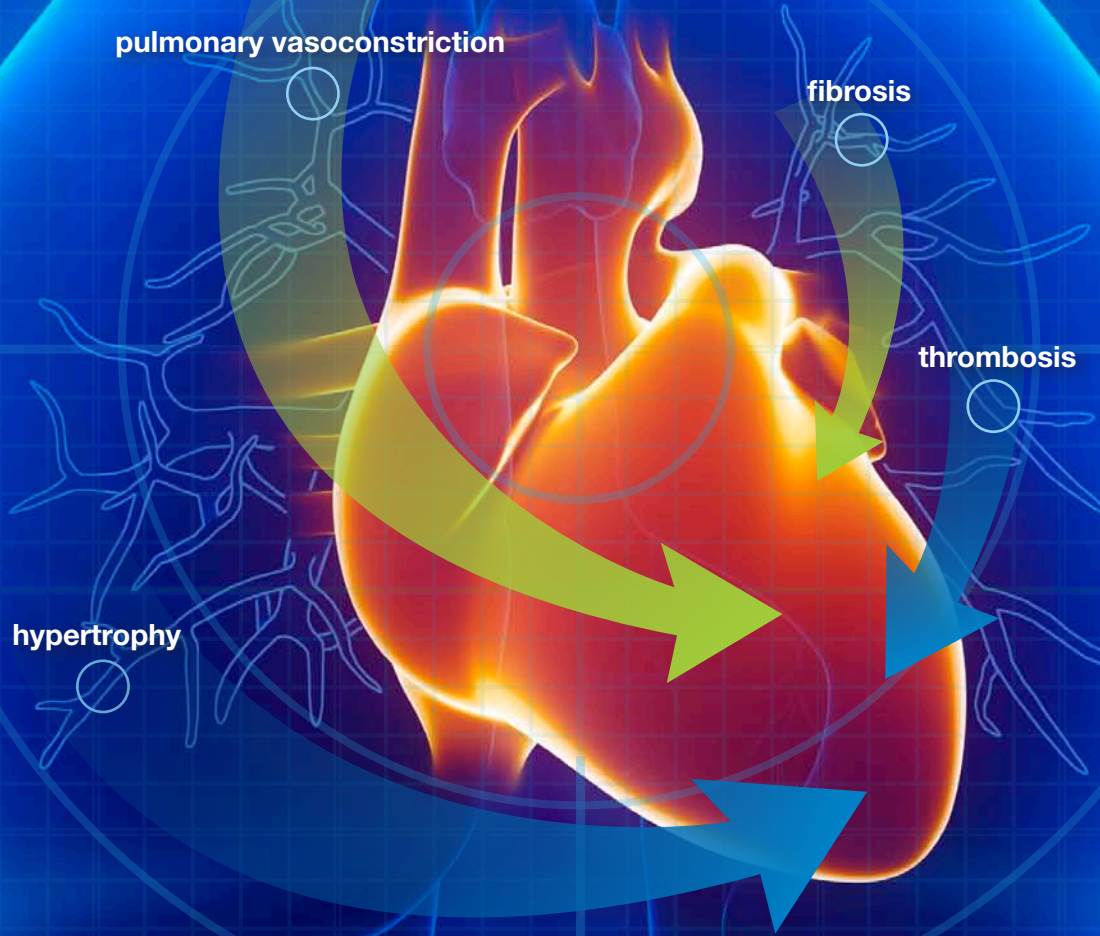
Evaluating AMD for Cost Savings Opportunities

Improving Star Ratings Through Clinical Outreach

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Pulmonary Arterial Hypertension and Pulmonary Fibrosis: Targeted Therapies to Improve Outcomes



Magellan Rx MANAGEMENT℠

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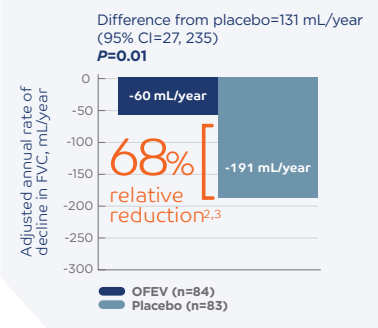
OFEV (nintedanib) is now recommended for the treatment of idiopathic pulmonary fibrosis (IPF) in the 2015 ATS/ERS/JRS/ALAT Clinical Practice Guideline[1*†]

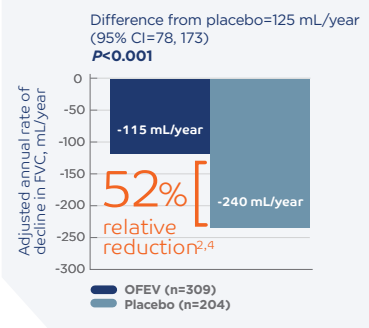
Slow the Path of IPF Progression for Your Members

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

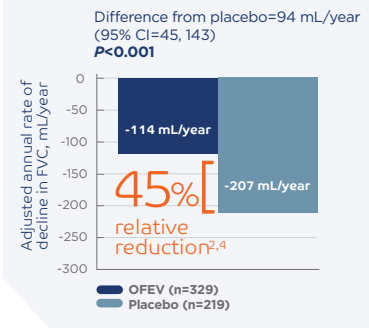
TOMORROW (Study 1)[2,3]



INPULSIS®-1 (Study 2)[2,4]



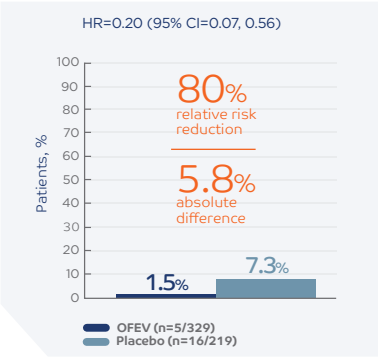
INPULSIS®-2 (Study 3)[2,4]



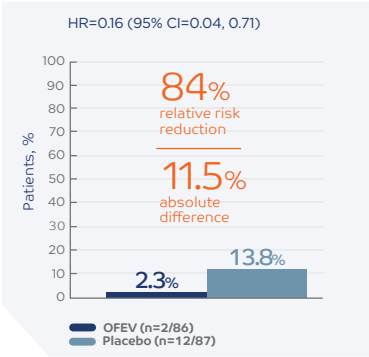
CI, confidence interval; FVC, forced vital capacity.
*Conditional recommendation for use; moderate confidence in effect estimates.[1]
†ATS, American Thoracic Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Association.
‡The annual rate of decline 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℠

Our Clinical Approach

Improving member health through targeted educational efforts designed to maximize safety, improve adherence and reduce gaps in care

At Magellan Rx Management we understand the complex and continuously evolving landscape surrounding health care and how our role as a prescription benefits manager is vital in helping our clients promote the safe, appropriate and cost-effective use of medications. We are focused on harnessing the power of our valuable data, innovative information technology systems and extensive clinical knowledge to hone in on opportunities to successfully improve health outcomes.

A Comprehensive Approach to Improved Member Health

Maximizing Safety

Offering a series of drug utilization review programs that focus on ensuring the highest level of patient safety:

- **Drug Interaction Alert Program**—Reduces the incidence of clinically significant drug-drug interactions through daily targeted prescriber notifications.
- **Geriatric RxMonitor Program**—Reduces the use of potentially inappropriate medications in elderly patients through targeted prescriber notifications, based on current national quality standards.
- **Narcotic Drug Utilization Reporting**–Minimizes unsafe narcotic analgesic use by identifying members who are receiving and filling narcotic prescriptions from multiple prescribers or pharmacies, or are taking a combination of narcotics that may not be safe.

Improving Medication Adherence

Communicating the importance of appropriate medication management and adherence:

- **Prescriber Outreaches**—Alert prescribers about patient-specific opportunities to improve medication adherence through a series of targeted, educational mailings on such topics as depression, osteoporosis, and cholesterol disorders.
- **Member Outreaches**—Improve medication compliance and adherence through targeted, educational mailings and interactive phone call reminders.

Reducing Gaps in Care

Addressing opportunities to improve the continuity of patient care:

- **Prescriber Outreaches**—Focus prescribers on opportunities that may exist to reduce gaps in patient care through a series of targeted, member reports and educational mailings on such topics as ACEI/ARB use and/or statin therapy, asthma management, and migraine prevention.
- **Member Outreaches**—Help members better understand the importance of controlling their medical condition and encourage lifestyle choices that promote good health. Each member outreach is coordinated with a report and educational piece mailed to the member's prescriber.

Providing Relevant & Actionable Education

Presenting key educational information:

- **Prescriber Outreaches**—Provide prescribers with pertinent, educational information and leading industry guidelines to help improve the lives of members.
- **Member Outreaches**—Provide utilizing members with insightful information on a variety of general health care topics, such as effective pain, sleep, allergy and cholesterol management, the appropriate use of antibiotics, understanding and maximizing the use of generics, among others.

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Magellan Rx MANAGEMENT

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Letter from Magellan Rx

Dear Managed Care Colleagues,

Susan Petrovas, RPh

For those of us who have been in the managed care industry for a number of years, it has been amazing to witness the innovation in pharmaceutical development over time. Just within recent years, pharmaceutical products have been introduced that have revolutionized the management of many difficult-to-treat medical conditions, such as cancer, cystic fibrosis, pulmonary hypertension, and hereditary angioedema. These various innovations provide the opportunity to improve patient care and sustain quality outcomes. However, alongside these innovations, we've also witnessed a substantial increase in cost of care that has become difficult to control from a managed care perspective.

With costs continuing to escalate, it is becoming increasingly important to develop novel strategies that are designed to reduce waste, minimize variations in care, align incentives, and improve quality of care. This is no easy task, especially when evaluating opportunities to more appropriately manage the medical benefit. Medical pharmacy products are becoming a major driver of health care resources and are a growing concern for managed care organizations. One potential opportunity to improve standardization of care and generate cost-savings related to medical pharmacy products is the development of a medical formulary.

Currently several managed care organizations, including Magellan Rx Management, are evaluating opportunities to implement medical formularies. For decades, health insurance providers have been utilizing formularies to reduce treatment variation and contain cost under the pharmacy benefit. Why can't the same level of control be placed on the medical benefit? With the current technology platforms at our disposal and greater physician accountability for the quality and cost of the care that they provide, we believe that medical formularies are not only attainable, but practical.

Magellan Rx Management is always looking for new and innovative strategies to improve quality of care and contain cost for our health plan, employer, and government clients. The development of medical formularies is just one of the initiatives that is currently being evaluated. Combining our medical, specialty, and pharmacy benefit expertise allows us to leverage our collective scale and experience to manage the total drug spend for our clients, while ensuring a clear focus on the specific clinical/financial needs of each individual customer.

If you have questions regarding any of the services offered by Magellan Rx Management, please feel free to contact me directly at **spetrovas@magellanhealth.com.** As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

Susan C. Petrovas, RPh
Magellan Rx Management

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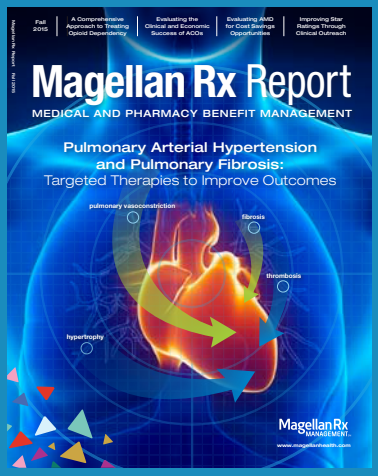

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WHEN CHOOSING A NOAC, IT'S TIME TO

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

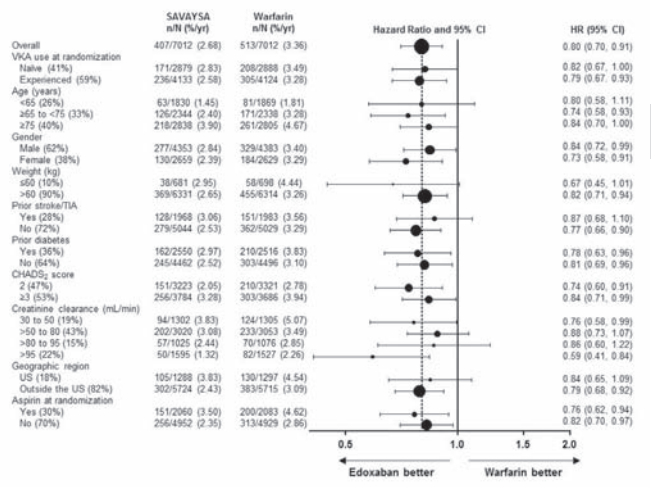
[b] Lower GI bleeding included anorectal bleeding

[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]*.

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MANAGED CARE NEWSSTAND

Major Precision Medicine Cancer Trial Underway

Enrollment for the National Cancer Institute's (NCI) phase II MATCH: Molecular Analysis for Therapy Choice trial is underway. In this landmark study, each patient will be matched with a therapy that targets a specific molecular abnormality in his or her tumor.

The trial will test more than 20 drugs or drug combinations that target specific genetic mutations. During screening, patients' tumors will be biopsied to identify genetic abnormalities that may be targeted by the drugs being studied. Enrolled patients will be treated with a targeted drug regimen for as long as their tumors remain stable or shrink.

The study will start with 10 substudies and will expand to include 20 substudies. Researchers have a goal of enrolling about 1,000 patients 18 years of age or older. To be eligible, patients must have lymphomas or solid tumors that continued to advance following standard treatment or tumors that have no standard therapy. As part of the study design, about 25 percent of enrolled patients will have rare cancers (cancers other than non-small cell lung, colon, breast or prostate cancers).

Source: ASCO, NCI announce plans for precision medicine trials. The American Society of Clinical Oncology. News release. June 1, 2015.

Prostate Cancer Treatment Trends Improving

A new study found that more doctors are treating men with low-risk prostate cancer with active surveillance or "watchful" waiting. In addition, men with high-risk prostate cancer are more likely to receive appropriate treatment that can potentially cure their disease.

Researchers analyzed data collected between 1990 and 2013 for the national Cancer of the Prostate Strategic Urologic Research Endeavor or CaPSURE™ registry. The more than 10,000 men included in the study had tumors classified as stage cT3aNoMo or lower and were treated with surgery, radiation, androgen-deprivation monotherapy, or active surveillance.

Watchful waiting of low-risk disease ranged from 7 to 14 percent between 1990 and 2009 before rising dramatically to 40 percent from 2010 to 2013. Treatment with androgen-deprivation monotherapy for men with intermediate- and high-risk tumors rose steadily from 1990, then decreased as more men began receiving more effective local treatment rather than androgen-deprivation therapy alone.

The authors reported: "The magnitude and speed of the changes suggest a genuine change in the management of patients with prostate cancer in the United States, which could accelerate as more clinicians begin to participate in registry efforts. Given that overtreatment of low-risk disease is a major driver of arguments against prostate cancer screening efforts, these observations may help inform a renewed discussion regarding early detection policy in the United States."

Source: Findings suggest improvement in management of localized prostate cancer. Journal of the American Medical Association. News release. July 7, 2015.

Study Suggests Mammography Screening Leads to Overdiagnosis

Researchers who conducted an ecological study of 16 million women in the United States found that mammography screening in the year 2000 led to an overdiagnosis of small cancers in the breast.

The study included women living in more than 500 counties who report to the Surveillance, Epidemiology and End Results program cancer registries. During 2000, 53,207 women were diagnosed with breast cancer and followed for 10 years to determine the correlation between rates of screening, the incidence of breast cancer, the size of tumors, and breast cancer mortality.

The researchers found that in the counties studied there was a correlation between screening rates and the incidence of cancer but not with breast cancer-related deaths. For example, they found that a 10 percent increase in screening led to a 16 percent rise in breast cancer diagnoses but no significant change in breast cancer mortality.

The authors say their findings suggest that screening mammography results in "widespread overdiagnosis" of small cancers without improving mortality.

Source: Detecting more small cancers in screening mammography suggests overdiagnosis. JAMA Internal Medicine. News release. July 6, 2015.

Study Supports Early HIV Treatment

The international Strategic Time of AntiRetroviral Treatment (START) study found patients infected with HIV who start antiretroviral drugs sooner are less likely to develop AIDS or other serious illnesses. This is the first large-scale randomized study to demonstrate that all HIV-infected patients can benefit from early treatment with antiretrovirals.

The study began in 2011 at 215 sites in 35 countries and was scheduled to conclude in 2016. More than 4,600 HIV-infected men and women who had never taken antiretroviral medications and who had CD4+ cell counts in the normal range were enrolled. About half of the participants received treatment, while treatment was deferred for the other half until their CD4+ levels dropped. An interim analysis found that early treatment reduced the risk of death or serious illness by 53 percent. The results were so clear that an independent board recommended releasing the data early.

The data from this and previous studies that showed that antiretroviral drugs also reduce the risk of transmission to uninfected sexual partners validate the current U.S. guidelines that recommend treatment for everyone infected with HIV.

Source: Starting antiretroviral treatment early improves outcomes for HIV-infected individuals. National Institutes of Health. News release. May 27, 2015.

Alternative Payment Models May Impact Personalized Medicine

The Personalized Medicine Coalition (PMC) has released a new white paper that explores the possible impact of alternative payment models on personalized therapies. The report, "Paying for Personalized Medicine: How Alternative Payment Models Could Help or Hinder the Field," stated that alternative payment models could support or impede the use of personalized therapies. The authors specifically looked at the influence of accountable care organizations, bundled payments, medical homes, and clinical pathways.

The paper noted: "The emergence of personalized medicine is eliciting growing excitement and optimism among patients, providers, and policymakers as a new wave of targeted therapies emerges and demonstrates the potential of the field to improve patient outcomes and health care delivery. At the same time, growing demands for health care cost containment are driving increased interest in 'alternative payment models,' as policymakers seek approaches that can balance care quality, cost containment, and physician-patient decision-making autonomy."

According to the authors, personalized medicine has the potential to make inroads in the treatment of illnesses ranging from cancer to Alzheimer's disease. They said it is vital that policymakers consider the impact of changing payment systems on biomedical breakthroughs. If all stakeholders work together, the report concluded, a more efficient, high-quality health care system is possible.

Source: Paying for personalized medicine: How alternative payment models could help or hinder the field. Personalized Medicine Coalition. White paper. April 23, 2015.

Review Finds Satisfaction Up, Costs Down for Members in PCMH

One health plan found that its patient-centered medical home (PCMH) programs are improving care and reducing costs for more than 750,000 participating members.

Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ) recently reported the 2014 results of its PCMH.

PCMH members with diabetes achieved a 6 percent higher rate of improved diabetes control and a 7 percent higher rate of cholesterol management when compared with members in traditional practices. PCMH members also had an 8 percent higher rate of colorectal cancer screenings and a 3 percent higher rate of breast cancer screenings.

Horizon reports that their patient-centered programs also reduced costs. Members in their PCMHs had an 8 percent lower rate of hospital stays and a 5 percent lower rate of visits to the emergency room. The total cost of care was 9 percent lower for those in the PCMH plans.

"The promise of patient-centered, or value-based, care to deliver better quality care at a lower cost is no longer theoretical, it's a reality," said Robert A. Marino, chairman and CEO of Horizon BCBSNJ.

Source: Patient-centered care continues to deliver on promise of better quality care at a lower cost. Horizon Blue Cross and Blue Shield of New Jersey. News release. Aug. 4, 2015.

Medication-Assisted Treatment: Bringing a Chronic Care Model to the Management of Opioid Addiction

Shareh Ghani, MD, Chief Medical Officer and Chief Solution Architect, Magellan Behavioral Health;
Gary M. Henschen, MD, Chief Medical Officer, Behavioral Health, Magellan Health Services

Shareh Ghani, MD

Gary M. Henschen, MD

Opioid addiction is a growing problem and has had devastating effects on patients, their families, and society. Currently there are 2 million Americans addicted to prescription opioids, with an additional 500,000 heroin addicts.[1] This crisis affects all segments of our society, and once patients are addicted, they experience permanent brain changes, which make opioid addiction a relapsing and chronic illness. Unfortunately, our health care system is currently organized in a manner to treat addiction with acute care services, with the hope of abstinence upon discharge. This treatment approach typically leads to poor health outcomes such as treatment failures, hospital admissions, and multiple hospital readmissions. Therefore, it is clear that in order to address this crisis we need to transition our philosophy on the treatment of opioid dependence, moving from an acute to a chronic perspective. Ultimately, chronic treatment saves money in the long run by reducing relapses and hospitalizations, thus also improving health outcomes.

Between 2007 and 2013, heroin abuse or dependence skyrocketed 150 percent, while overdose deaths nearly doubled between 2011 and 2013; a majority of overdoses included multiple substances such as cocaine, alcohol, marijuana, and opioid pain relievers.[2] In 2013, 59 percent of the 8,257 overdoses related to heroin in the United States involved at least one other drug.[2] Opioid dependence was considered the strongest risk factor that contributed to heroin abuse. Polysubstance use is considered a factor that should be examined during the creation and implementation of prevention policies. This increase is occurring among people of all income and most age levels, with the greatest increases seen in women and those with private insurance and higher incomes.[2] In 2007, the number of deaths involving opioids was 5.28 times the number involving heroin.[3] From 1996 to 2007, unintentional overdoses from methadone increased 468 percent, while almost none were from buprenorphine.[3]

In addition, there remains a huge gap in care. In 2013, 22.7 million people age 12 or older required treatment for drug and/or alcohol abuse.[4] Of these patients, 2.5 million received treatment at a specialty facility.[4] Therefore, 20.2

Table 1 Health Care Resource Use of Opioid Abusers[8]

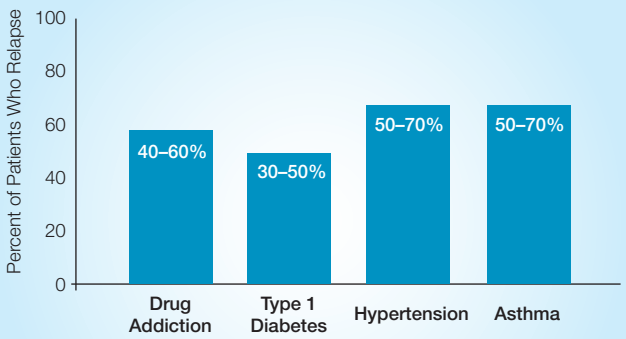
Costs (2012 Dollars)	Abusers	Controls
Inpatient	$10,011	$3,212
Emergency Department	$1,885	$616
Outpatient	$7,386	$4,603
Prescription Drug	$3,019	$2,494

million patients needed treatment, but did not receive treatment at a specialty facility.[4] If more patients continue to not receive treatment, and more programs are not implemented to help these patients, the number of untreated patients will continue to escalate. In addition, providers do need to be aware of this epidemic, and although responsible prescribing can save lives, the amount of prescription opioids prescribed has quadrupled from 1999 to 2013.[5]

Opioid abuse costs payors at least $72.5 billion a year and adds an extra $1.71 per-member per-month (PMPM) to employer health care costs.[6,7] This makes addressing opioid abuse a critical issue for payors. Table 1 depicts the increased resource use in abusers versus health plan members who do not abuse opioids — considered controls — among commercially insured health plans.

Despite the prevalence and cost of opioid abuse in this country, treatment remains suboptimal. About half of those treated relapse within a year, and within five years, only about one-fourth remain in recovery.[9,10]

Figure 1: Comparison of Relapse Rates Between Drug Addiction and Other Chronic Illnesses[12]



Relapse rates for people treated for substance use disorders are compared with those for people with diabetes, hypertension, or asthma. Relapse is common and similar across these illnesses (as is adherence/non-adherence to medication). Thus, drug addiction should be treated like any other chronic illness; relapse serves as a trigger for renewed intervention.

Substance Abuse as a Chronic Health Condition

Substance abuse is similar to other chronic diseases in several ways[11]:

- It has biological and behavioral components, each of which must be addressed during treatment.
- Recovery is a long-term process requiring repeated episodes of treatment.
- Relapses often occur, requiring treatment adjustments. In fact, relapse rates for substance abuse are similar to those for other chronic illnesses (see Figure 1).
- Participating in support programs during and after treatment can facilitate recovery, or at least help manage the disease.

Embracing a chronic health care model instead of an acute care model allows for the recognition and acceptance of opioid addiction as a chronic illness, providing an evidence-based framework to increase quality of care, reduce costs, and improve health outcomes. This requires:

- A culture, organization, and mechanisms that promote safe, high-quality care
- The delivery of effective, efficient clinical care, and self-management support
- Clinical care that is consistent with scientific evidence and patient preferences
- The availability of patient and population data to facilitate efficient and effective care
- Empowering and preparing patients to manage their health and health care
- Mobilizing community resources to meet the needs of patients

Several studies suggest that adopting a chronic care approach for the treatment of substance abuse can improve outcomes compared with usual care, particularly when treatment involves a primary care physician.[9,10,13,14] Indeed, a workshop sponsored by the National Quality Forum found enough evidence supporting the use of a chronic care model for patients with substance abuse problems to call for their long-term, ongoing management in a primary care setting.[14]

However, the only randomized controlled trial found no difference in relapse rates between those receiving chronic care management and those receiving usual care. The Addiction Health Evaluation and Disease Management (AHEAD) trial enrolled 563 individuals with substance abuse disorders, including opioid addiction. The intervention consisted of longitudinal care for sub-

Embracing a chronic health care model instead of an acute care model allows for the recognition and acceptance of opioid addiction as a chronic illness, providing an evidence-based framework to increase quality of care, reduce costs, and improve health outcomes. Health plans are in an ideal position to encourage the use of MAT for their members and to develop programs that integrate substance abuse treatment into primary care.

stance dependence and related medical and psychiatric comorbidities provided in a primary care setting and involving medical, psychiatric, and addiction clinicians. Individuals were also offered medication to treat their addiction.[15] The authors did not report how many participants received medication.

While the results were surprising and disappointing, an editorial in the *Journal of the American Medical Association* cautioned against extrapolating them across the entire field, noting that those enrolled in the study were "clinically and socially complex." Most had multiple dependencies and significant psychiatric and medical comorbidities, and many were homeless or recently incarcerated.[15,16]

Effective Treatment for Substance Abuse Disorders: Medication-Assisted Treatment

The Magellan Rx Management medication-assisted treatment (MAT) program focuses on utilizing proven medications to treat members with opioid dependency. The program not only focuses on patients who have been discharged from inpatient treatment programs, but also patients receiving outpatient case or disease-management services. Magellan monitors the number of physicians prescribing MAT medications, buprenorphine (with or without naloxone), naltrexone, or methadone, and tracks patient readmission rates.

Buprenorphine is a partial opioid agonist and mixed opioid agonist-antagonist usually provided in a formulation that includes naloxone, which reduces the risk of misuse. Naltrexone is an opioid antagonist that blocks the effects of opioids, while methadone is a synthetic opioid.[17]

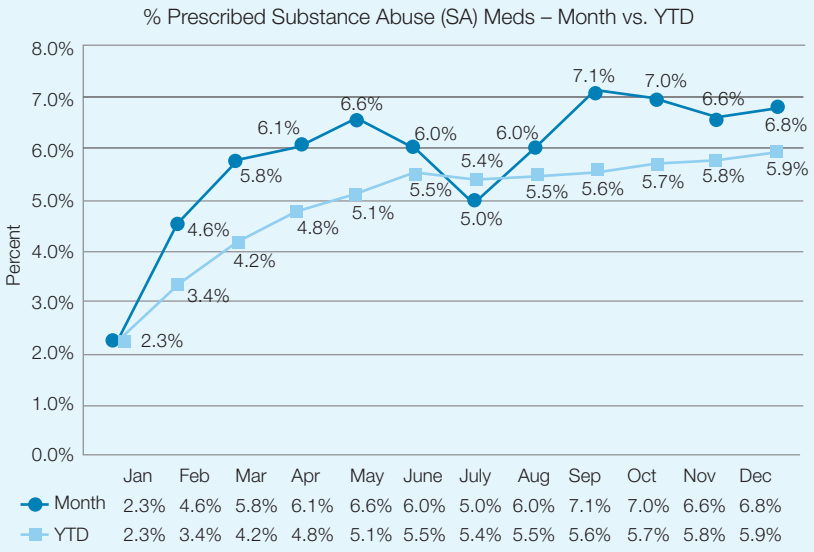
While naltrexone can be prescribed by all physicians, those prescribing buprenorphine in their offices must receive a waiver after completing a course on appropriate prescribing, or be board certified in addiction medicine or addiction psychiatry. They are limited to treating 100 patients at a time and must refer patients for counseling and other nonpharmacologic therapies.[18,19] Methadone can only be administered in outpatient treatment programs authorized at the federal and state level.

Numerous studies attest to the cost-effectiveness of MAT, with every dollar spent on treatment resulting in a savings of $1.80.[19-22] These savings imply that transitioning approximately 10 percent of untreated patients in New England into treatment would generate over $550 million in savings.[19-22] One study found that office-based MAT with buprenorphine-naloxone cost $35,100 for every quality-adjusted life year (QALY) saved.[23] In addition, a U.S. study within the Medicaid population found that maintenance therapy with buprenorphine cost $1,330 less than methadone.[24]

Despite dozens of studies attesting to the efficacy of MAT combined with psychosocial treatment versus psychosocial treatment alone, as well as its cost-effectiveness, less than half of the 2.5 million Americans with opioid addictions are currently receiving MAT.[22,25] The shortage is so acute that the Substance Abuse and Mental Health Services Administration recently announced it would provide $11 million in funding to 11 states to expand their ability to provide MAT and coordinated psychosocial services to people with opioid use disorders.[26]

In May 2015, the American Society of Addiction Medicine released its first guidelines on the use of medications to treat opioid addiction. They provide recommendations as to the most appropriate medication and treatment ven-

Figure 2: Prescriptions for MAT with a Chronic Care Management Approach[3]



ue for patients based on their medical and social history, and highlight the importance of concurrent psychosocial treatment that includes a psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services.[17]

Poor Access to MAT

Currently, about 65 percent of patients taking buprenorphine receive the drug in a physician's office, while the rest receive it in a methadone clinic.[27] Yet office-based MAT, while not appropriate for everyone, avoids the stigma of treatment in a methadone clinic, with studies finding similar or better efficacy with buprenorphine treatment compared to methadone.[28-37]

However, there are numerous barriers to the use of office-based MAT, including a lack of coverage, treatment duration or dosage limitations, prior authorization, and step-therapy requirements.[38]

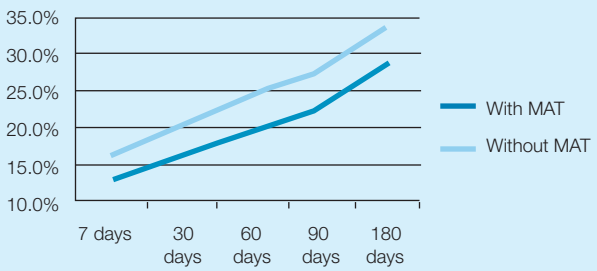
One major barrier is a shortage of waivered providers, with just 2 percent of U.S. physicians able to prescribe buprenorphine in their offices as of 2012.[39] The shortage is particularly acute in rural areas, which have high rates of opioid dependency.[39]

While the percentage of counties with a shortage of waivered physicians fell from nearly 100 percent in 2002 to 46.8 percent in 2011, an estimated 26 percent of the population resides in a treatment shortage county, mostly in the Midwest.[39] As the authors of one study noted, "Obtaining opioid agonist treatment remains challenging in large swaths of the United States."[39]

In addition, a substantial percentage of waivered physicians still do not offer the treatment in their offices, primarily because of a lack of institutional support and limited access to psychosocial services for their patients.[40]

Figure 3: Readmission Results with and Without MAT[3]

	Number of Readmissions										
	Discharged	Within:									
		7 days		30 days		60 days		90 days		180 days	
		#	%	#	%	#	%	#	%	#	%
With MAT	1,051	134	12.7%	169	16.1%	203	19.3%	234	22.3%	303	28.8%
Without MAT	20,487	3,273	16.0%	4,135	20.2%	4,957	24.2%	5,619	27.4%	7,002	34.2%



Role of Health Plans in MAT

Health plans are in an ideal position to encourage the use of MAT for their members and to develop programs that integrate substance abuse treatment into primary care. Health plans' access to claims data identifying members at risk for substance abuse allows for the introduction of case management approaches similar to those provided to individuals with other chronic diseases such as diabetes and congestive heart failure.

Magellan Rx Management created a MAT Initiative which included the following[3]:

- Developed procedures to capture use of MAT medications within claims system
- Obtained 2010 baseline data (June to December 2010)
- Developed outcome measures (increase in use of MAT medications and readmission data)
- Trained clinical and medical staff for peer-to-peer discussions to increase use of MAT
- Created internal benchmarks for use of MAT
- Created a MAT medication guideline for staff
- Established research and other educational material postings on our provider website
- Numerous provider and member communications through webinars, newsletters, emails, and website postings
- Included MAT expectations in our provider handbook and Medical Necessity Criteria
- Initiated national quality improvement study for National Committee for Quality Assurance (NCQA)

One large health plan that implemented a Magellan Rx Management MAT program experienced a significant increase in the use of MAT medications (see Figure 2).[3] From January 2011 through December of implementation, outcome measurements indicated that 5.9 percent of substance abuse discharges had been placed on MAT medications year-to-date in 2011, which correlated to a reduction in relapse.[3] In addition, other results by level of care have shown that independent providers increased MAT prescribing by 5.3 percent, residential treatment facilities by 5.5 percent, partial hospitalization programs by 9.2 percent, and independent outpatient facilities by 5.9 percent.[3] Figure 3 delineates that members receiving MAT had significantly fewer readmissions (28.8 percent) versus those not receiving MAT (34.2 percent) in the year after program implementation.

A Need Still Exists

There still exists a need to improve MAT programs to focus on a chronic disease care model. Magellan Rx Management is completely redesigning its MAT program and additional initiatives are being explored. Current practices are being evaluated and cutting-edge recommendations are being provided regarding MAT, and there is a plan to then implement across the country. The goal is to identify patients with substance abuse/comorbidities and provide biological treatment through medications. Patients will be identified through inpatient hospitalizations/readmissions with comorbid alcohol/drug-use disorder. If the member is not on a MAT medication, then outreach will be made to the provider to educate on MAT use. The outcomes that will be tracked are the readmission rates of patients put on MAT versus those who are not; success will be defined as improving patient quality of life and reducing hospitalizations/readmissions.

There are six components being evaluated to enhance the MAT program:

- Changes to Care Coordination — Enhancing MAT, risk stratification of patients who could utilize MAT
- MAT Reporting — Changing from a process measure to an outcome measure
- Network Sufficiency of MAT Providers
- Quality Oversight and Monitoring — Medication Action Plans for patients and coordination of care
- Training — Internal training for providers on how to use reports generated by Magellan Rx Management
- Incorporation of MAT into Medical Action Plans and Cost of Care

Conclusion

The dual epidemic of prescription pain reliever and heroin abuse shows no sign of abating. The epidemic is increasingly shifting from a marginalized population (homeless, incarcerated, low socioeconomic status) to a more inclusive segment of the population, including women and higher-income, commercially insured individuals, as well as Medicare recipients.[41]

Traditional efforts to treat substance abuse — primarily psychosocial approaches such as 12-step programs, abstinence, and psychotherapy — have high rates of relapse. Adding MAT with buprenorphine (with or without naloxone), naltrexone, or methadone demonstrates greater effectiveness than psychosocial approaches alone, with significant cost-savings.

Payors are in an ideal position to bring a chronic care management model to the treatment of substance abuse, using a comprehensive approach that includes case management, medical and mental health services, community support, and primary care clinician involvement.

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Pulmonary Arterial Hypertension: New Therapies, Guidelines Seek to Improve Outcomes

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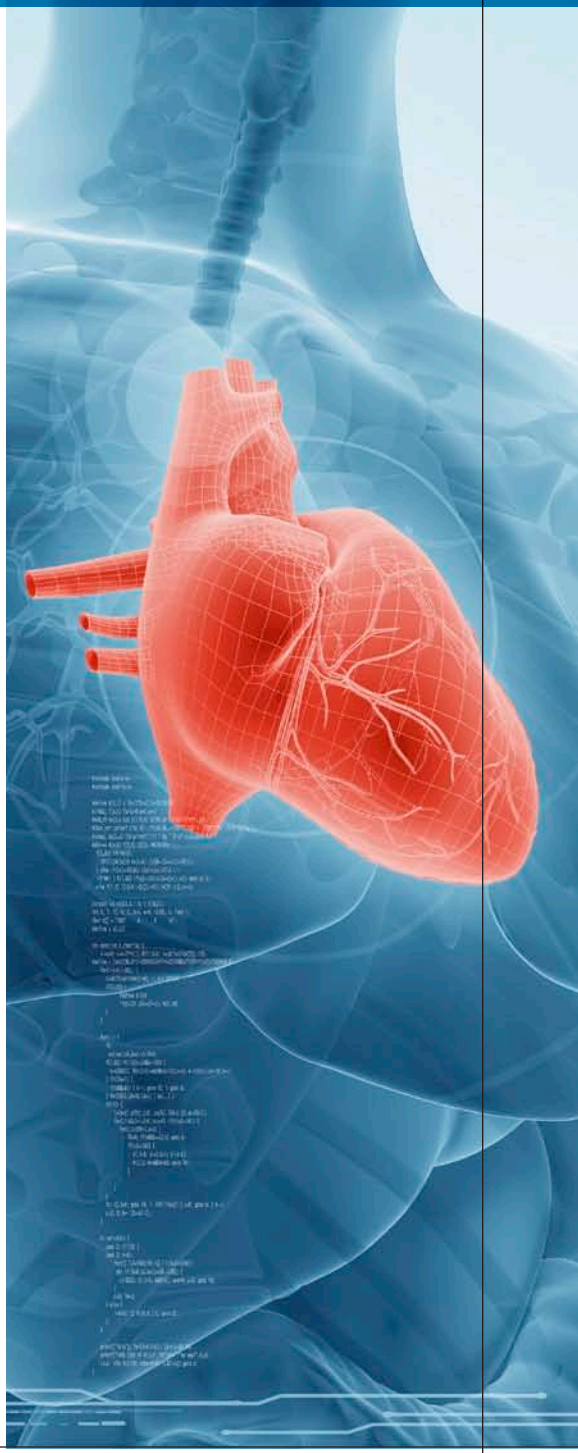
Despite the recent introduction of new pharmacologic therapies and treatment guidelines, the clinical and economic burden of pulmonary arterial hypertension (PAH) remains substantial.[1,2] PAH is a rare, progressive, and life-threatening form of pulmonary hypertension (PH). PAH is characterized by elevated pulmonary arterial pressure (PAP) and increased pulmonary resistance (PVR), leading to right ventricular hypertrophy, dysfunction, and eventual right ventricular heart failure.[2] Drugs developed to target three different pathways in the treatment of PAH are endothelin receptor antagonists (ERAs), prostacyclin analogs, and phosphodiesterase-5 (PDE5) inhibitors.[3] PAH remains incurable and survival rates are unacceptably low, highlighting the need for improved disease awareness and evidence-based guidelines, as well as further clinical trial data to help fulfill the need for early intervention and therapies that can be used to improve health outcomes.

PAH Incidence, Prevalence

Registries in the United States and abroad play an important role in better understanding the epidemiology of PAH.[3] A French registry estimated annual incidence of 2.4 cases per million individuals and prevalence of 15.0 cases per million individuals.[4] Analysis of the U.S. Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management, known as REVEAL, estimated incidence of 2.0 individuals per million per year and a prevalence of 10.6 cases per million individuals.[5] Other prevalence estimates range as high as 52 cases per million.[5]

PAH is more common in certain groups of patients, with females representing 70 to 80 percent of PAH patients in the United States.[5,6] Individuals with connective tissue disease and congenital heart disease also may be at a higher risk for PAH.[7] Diagnosis of PAH often occurs late when disease is already quite advanced, and the prognosis for patients with PAH is poor.[4,5,8] PAH significantly impacts patient quality of life (QOL) and health-related QOL (HRQOL), and the five-year survival rate is 57 percent.[9,10]

The REVEAL database has yielded important information on patients who are hospitalized for PAH. Patients hospitalized for pulmonary hypertension have advanced disease, are likely to be rehospitalized, and have a poor prognosis. The risk of rehospitalization was greater and the survival rate



at three years was worse.[11] PAH hospitalizations are costly. An analysis of Medicare Advantage and commercially insured patients with PAH showed an average length of stay (LOS) of 16.21 days and mean cost of $73,880. Similar findings have been demonstrated in other studies.[12]

Table 1 World Health Organization 2013 Updated Classification of Pulmonary Hypertension[3]

1	**Pulmonary arterial hypertension**
1.1	Idiopathic PAH
1.2	**Heritable PAH**
1.2.1	BMPR2
1.2.2	ALK-1, ENG*, SMAD9*, CAV1*, KCNK3*
1.2.3	Unknown
1.3	**Drug and toxin induced**
1.4	**Associated with:**
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1'	**Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis**
1"	**Persistent PH of the newborn***
2	**Pulmonary hypertension due to left heart disease**
2.1	Left ventricular systolic dysfunction
2.2	Left ventricular diastolic dysfunction
2.3	Valvular disease
2.4	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies*
3	**Pulmonary hypertension due to lung diseases and/or hypoxia**
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental lung diseases
4	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
5	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1	Hematologic disorders: chronic hemolytic anemia*, myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH*

* 2013 updates
ALK1 = activin receptor-like kinase type; BMPR2 = bone morphogenetic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; KCNK3 = potassium channel, two pore domain subfamily K, member 3; SMAD9 = mothers against decapentaplegic homolog 9

Pulmonary hypertension is defined and categorized by the 2013 Pulmonary Hypertension clinical classification by the World Health Organization (WHO) clinical classification system (Table 1).[13] Pulmonary arterial hypertension (WHO Class 1) is defined by a mean pulmonary artery pressure > 24 mmHg in the absence of pulmonary venous hypertension (wedge pressure) as measured by right heart catheterization. Causes include genetic and environmental factors,[13] congenital heart disease, connective tissue disease (scleroderma), drug toxicity, and idiopathy. Symptoms of PAH, which is most commonly reported in adults as idiopathic and heritable, may include dyspnea, dizziness, angina pectoris, syncope and near-syncope, edema, and cough.[1,13,14]

PAH Screening, Diagnosis, Care

Both WHO and the American College of Chest Physicians (ACCP) emphasize the need for early identification of PAH. Specifically, the guidelines updated in 2014 by ACCP call for an evaluation that uses a combination of WHO function class (FC), exercise capacity, echocardiographic, laboratory, and hemodynamic variables.[1] ACCP strongly advises definitive confirmation of the diagnosis of PAH prior to institution of therapy.

An early and accurate diagnosis followed by aggressive therapy may have a significant effect on patient outcome. One study of patients with a PAH diagnosis who were referred by cardiologists or pulmonologists to large university-based tertiary care centers during 2010 to 2011 found that 33 percent were misdiagnosed, 30 percent had received PAH-specific medications before referral, and 57 percent of prescribed medications were contrary to published guidelines.[15]

ACCP guidelines should be used only for treating PAH (WHO Class 1) patients; patients with PH (WHO Class 2 through 5) will not benefit from the recommended PAH therapies.

The diagnosis and management of PAH patients is complex and requires a collaborative effort between a patient's primary care physician, cardiologist, pulmonologist, rheumatologist, and other specialists at centers with expertise in PAH care.

The Pulmonary Hypertension Association (PHA) recently launched an accreditation program designed to raise the level of care for PH patients. At the time of publication, PHA was still accepting and processing applications for Center of Comprehensive Care (CCC) accreditation. CCC accreditation requires use of PAH consensus

guidelines and treatment with Food and Drug Administration (FDA) therapies. Twenty-six organizations, including PH programs at large organizations such as Brigham and Women's Hospital, Mayo Clinic, University of Texas Southwestern Medical Center, and Stanford University, have been accredited.[16] PHA also plans to offer Regional Clinical Program (RCP) accreditation beginning in 2016. RCPs must provide expert treatment of PAH patients with all nonparenteral therapies and collaborate with CCCs by referring patients.[16] In addition to accreditation, PHA aims to develop a national PAH patient registry to support clinical research and define and promote standards of care that improve patient outcomes.[17]

ACCP Treatment Guidelines

ACCP has developed extensive treatment guidelines that address pharmacologic therapy for symptomatic PAH patients and management strategies for asymptomatic patients with PAH treatment.[1] As seen in Table 2, the guidelines are specific for the clinical severity of PH as classified by WHO; the classification is based on functional status of the patient, ranging from Functional Class I (FC I), in which PAH does not affect day-to-day activities, to FC IV, in which patients are severely functionally impaired with resting symptoms. The limited nature of available evidence to support high-level recommendations led to a combination of recommendations and consensus statements. The treatment guidelines are designed to provide control of symptoms such as dyspnea, improve exercise endurance and functional capacity, as well as slow disease progression and worsening. The six-minute walk test is frequently used to monitor efficacy of therapy and determine which patients may need more aggressive pharmacotherapy.

Table 2 World Health Organization Functional Classification of Patients with Pulmonary Hypertension[1]

Classification	
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

FC I

For asymptomatic PAH patients (FC I) and at-risk patients (e.g., patients with systemic sclerosis or the presence of a known mutation), ACCP recommends continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy.[1] Contributing causes of PH, such as sleep apnea and systemic hypertension, in patients with PAH also should be treated aggressively.[1] The guidelines call for symptomatic PAH patients to undergo acute vasoreactivity testing and receive oral calcium channel blocker (CCB) therapy as appropriate.[1] Response to CCBs in nonidiopathic (IPAH) patients is low, and acute vasoreactivity testing must be individualized.

FC II

Key recommendations for patients with FC II symptoms, who are not candidates for CCBs or who have failed CCB therapy, include initiation of monotherapy with a currently approved ERA to stop the harmful effects of endothelin, a hormone that helps control blood flow and

Table 3 Indications, Administration, and Costs of Oral Therapies for PAH[1-3, 34]

Product Name	Dosing	How Supplied	WHO Classification	WAC/Month	WAC/Year
Letairis® (ambrisentan)	5 mg to 10 mg QD	5 mg and 10 mg tablets	WHO Group I	$7,368	$89,644
Revatio® (sildenafil)	5 mg or 20 mg TID	20 mg tablets	WHO Group I	$2,734	$33,264
Adcirca® (tadalafil)	40 mg QD	20 mg tablets	WHO Group I	$2,502	$30,441
Tracleer® (bosentan)	62.5 mg to 125 mg BID	62.5 mg and 125 mg tablets	WHO Group I	$8,220	$100,010
Opsumit® (macitentan)	10 mg QD	10 mg tablets	WHO Group I	$7,185	$87,418
Adempas® (riociguat)	1 mg to 2.5 mg TID	0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets	WHO Group I	$8,189	$99,633

Key: QD = once daily; TID = three times daily; BID = twice daily; WHO = World Health Organization; WAC = wholesale acquisition cost

The diagnosis and management of PAH patients is complex and requires a collaborative effort between a patient's primary care physician, cardiologist, pulmonologist, rheumatologist, and other specialists at centers with expertise in PAH care.

cell growth in blood vessels; PDE5 inhibitor to relax the muscles and reduce abnormal cell growth in blood vessels; or the soluble guanylate cyclase stimulator riociguat.[1] More specifically in these patients, ACCP guidelines include[1]:

- Letairis® (ambrisentan), Revatio® (sildenafil), or Adcirca® (tadalafil) to improve six-minute walk distance (6MWD)
- Tracleer® (bosentan) to delay time to clinical worsening and improve cardiopulmonary hemodynamics
- Opsumit® (macitentan) to delay the time to clinical worsening
- Adempas® (riociguat) to improve 6MWD, improve WHO FC, delay the time to clinical worsening, and improve cardiopulmonary hemodynamics

ACCP also suggests that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment of naïve PAH patients with WHO FC II symptoms, or as second-line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals.

FC III

Guidelines for treatment of patients with WHO FC III symptoms who are not candidates for CCBs or who have failed CCB therapy include initiation of monotherapy with a currently approved ERA, PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat.[1] More specifically in these patients, ACCP guidelines include[1]:

- Tracleer (bosentan) to improve 6MWD, decrease hospitalization related to PAH in the short term, and improve cardiopulmonary hemodynamics
- Letairis (ambrisentan) to improve 6MWD
- Opsumit (macitentan) to improve WHO FC and delay time to clinical worsening
- Revatio (sildenafil) to improve 6MWD, WHO FC, and cardiopulmonary hemodynamics
- Adempas (riociguat) to improve 6MWD, improve WHO FC, delay the time to clinical worsening, and improve cardiopulmonary hemodynamics

FC III, naïve PAH patients

For treatment of naïve PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease or other markers of a poor clinical prognosis, ACCP advises consideration of initial treatment with a parenteral prostanoid. More specifically in these patients, ACCP guidelines include[1]:

- Continuous IV Flolan® (epoprostenol) to improve FC, 6MWD, and cardiopulmonary hemodynamics
- Continuous IV Remodulin® (treprostinil) to improve 6MWD
- Continuous subcutaneous Remodulin (treprostinil) to improve 6MWD and cardiopulmonary hemodynamics

Similarly, for PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, ACCP guidelines suggest adding a parenteral or inhaled prostanoid. This includes IV Flolan to improve FC, 6MWD, and cardiopulmonary hemodynamics, and IV Remodulin to improve 6MWD and cardiopulmonary hemodynamics. In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5 inhibitor, the guidelines suggest the addition of inhaled Remodulin to improve 6MWD.[1] The addition of inhaled Ventavis® (iloprost) for PAH patients who remain symptomatic on stable and appropriate doses of an ERA or a PDE5 inhibitor may improve WHO FC and delay the time to clinical worsening.[1]

FC IV

ACCP guidelines for treating naïve PAH patients in WHO FC IV include initiation of monotherapy with a parenteral prostanoid agent. More specifically these patients should receive:

- Continuous IV Flolan (epoprostenol) to improve WHO FC, 6MWD, and improve cardiopulmonary hemodynamics
- Continuous IV Remodulin (treprostinil) to improve 6MWD
- Continuous subcutaneous Remodulin (treprostinil) to improve 6MWD and cardiopulmonary hemodynamics

Naïve PAH patients in WHO FC IV who are unable or do not desire to manage parenteral prostanoid therapy should be treated with an inhaled prostanoid in combination with an ERA (e.g., Tracleer to improve 6MWD and cardiopulmonary hemodynamics; inhaled Ventavis to improve 6MWD WHO FC; inhaled Tyvaso® [treprostinil, in combination only] to improve 6MWD).[1]

The updated guidelines also address the use of combination therapy and dose modifications.[18] WHO experts recommend combination therapy to achieve treatment goals, and the REVEAL registry data show that many PAH centers in the United States have been treating patients with dual or triple therapy.[19,20] ACCP recommends that a second class of PAH therapy be added to improve exercise capability for WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy. A third class of therapy may be added if patients experience unacceptable or deteriorating clinical status following the second class of therapy. ACCP recommends these patients receive evaluation at centers with expertise in complex PAH treatment.[1]

Supportive Therapies

PAH patients also may require more conventional therapies to treat comorbidities. These therapies include diuretics, anticoagulants, oxygen, and digoxin. The COMPERA study showed a significantly better three-year survival (p=0.006) in patients with IPAH on anticoagulants compared with patients who did not receive anticoagulants.[21] Nonpharmacologic measures such as diet, exercise, and physical rehabilitation, along with appropriate vaccination, also may be recommended.[21]

Implications for Managed Care

Determining the most appropriate and cost-effective treatment for PAH presents many challenges for managed care. While there are 13 specialty agents that may offer improvement in long-term morbidity and mortality approved for use in the United States, PAH remains a progressive and incurable disease that is difficult to diagnose.[5] Long-term clinical trials for PAH therapies have been hampered by the disease's high morbidity, instead focusing on single markers such as 6MWD during short-term trials.[22] The number of patients diagnosed with PAH is also relatively small.

The limited number of PAH patients, recent release of new treatment guidelines, and introduction of new therapies also complicate cost estimates for treating PAH. For example, annual costs for sildenafil, bosentan, ambrisentan, and iloprost were estimated at $12,761, $55,890, $56,736, and $92,146, respectively; annual costs for weight-based dosages of epoprostenol and treprostinil were estimated at $33,153 and $97,615, respectively.[23] Data from Massachusetts related to the average cost per claim of generic or brand PAH drugs showed prostanoids such as iloprost and reprostinil tablet topped $20,000 and $30,000 respectively.[24]

Effectiveness and efficiency can be improved by emphasizing the proper timely diagnosis, based on guideline criteria and evaluation/testing at centers with PAH expertise. This will, in turn, ensure the correct initiation, selection, and administration of treatment for PAH patients and avoid unnecessary and potentially harmful treatment of individuals with other subcategories of PH.[1] In addition, nurse clinicians play a critical role in managing PAH patients by providing education about the disease and available therapies, titrating medications, monitoring side effects, and recognizing complications.[25] Payors may also use specialty pharmacies to help patients better manage their PAH by providing educational materials, easy access to clinical experts, and adherence programs. This high-touch approach may be particularly important given that the oral, inhaled, and parenteral routes for PAH therapies are associated with frequent dosing and monitoring.

Future Directions

A new drug to treat PAH, oral Uptravi® (selexipag), is expected to reach the U.S. market in 2016.[26] Uptravi, which is a selective IP prostacyclin receptor agonist, decreased the risk of morbidity/mortality versus placebo by 40 percent in a large, phase III clinical trial.[27,28] Patients already receiving treatment for PAH, including those already on combination therapy, were among those who the research showed benefited from Uptravi.[28] Approval of the drug is expected to drive growth in the prostacyclin and prostacyclin analogs market.[26]

Overall, research into PAH interventions is robust with the U.S. National Institutes of Health reporting 423 studies.[29] The studies include research related to the use of dietary supplements, drugs, and screening and analysis of biomarkers. Drug-device combination products that, for example, deliver pulsed, inhaled nitrous oxide (iNO) or IV delivery of treprosinil, also are in development.[30, 31] Cell-based therapies are also being studied to determine whether genetically enhanced stem cells may be able to repair and regenerate lung blood vessels in PAH patients.[32] In addition, use of epigenetic technologies in PAH research has been suggested as a method for better understanding the disease and developing new drugs and other treatment options.[33]

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LET HIM EXPLORE

WITH ELOCTATE, THE FIRST AND ONLY rFVIII WITH A PROLONGED HALF-LIFE

Selected Important Safety Information

- ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis

GET TO KNOW ELOCTATE

ABR

Median overall annualized bleed rate (ABR) of

1.6 *†

(0.0, 4.69)‡

BLEED CONTROL

0 BLEEDS in **45%** of subjects*†

DOSING

Routine prophylaxis starting interval of

EVERY 4 DAYS§

rFVIII=recombinant Factor VIII.

*A-LONG, a multicenter, prospective, open-label, Phase 3 study (N=165) evaluating the safety and efficacy of ELOCTATE in previously treated male patients (aged 12-65 years) with severe hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe hemophilia A) that compared the efficacy of each of 2 prophylactic treatment regimens (individualized interval [n=117] and fixed weekly [n=23]) to episodic (on-demand [n=23]) treatment. Hemostatic efficacy was determined in treatment of bleeding episodes and during perioperative management in subjects undergoing major surgical procedures. 164 and 163 subjects were evaluable for safety and efficacy, respectively. 146 and 23 subjects were treated for at least 26 weeks and 39 weeks, respectively.

†In the individualized prophylaxis arm (n=117) of the A-LONG clinical trial.

‡Median (interquartile range 25th-75th percentiles).

§**Recommended prophylaxis starting dose of 50 IU/kg every 4 days, with adjustments based on patient response in the range of 25-65 IU/kg at 3- to 5-day intervals. More frequent or higher doses up to 80 IU/kg may be required in children <6 years of age.**

Indications and Important Safety Information

INDICATIONS: ELOCTATE [Antihemophilic Factor (Recombinant), Fc Fusion Protein] is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: control and prevention of bleeding episodes, perioperative management (surgical prophylaxis), and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ELOCTATE is not indicated for the treatment of von Willebrand disease.

CONTRAINDICATIONS: ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

WARNINGS AND PRECAUTIONS: Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Immediately discontinue ELOCTATE and initiate appropriate treatment if hypersensitivity reactions occur. Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Patients using ELOCTATE should be monitored for the development of Factor VIII inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor VIII levels have been achieved and maintained.

ADVERSE REACTIONS: Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

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

ELOCTATE®
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

Biogen

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ELOCTATE™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein]
Lyophilized Powder for Solution For Intravenous Injection.

Brief Summary of Full Prescribing Information.

1 INDICATIONS AND USAGE

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:

- Control and prevention of bleeding episodes,
- Perioperative management (surgical prophylaxis),
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ELOCTATE is not indicated for the treatment of von Willebrand disease.

4 CONTRAINDICATIONS

ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, suspect the presence of an inhibitor (neutralizing antibody). [*see Monitoring Laboratory Tests* (5.3)]

5.3 Monitoring Laboratory Tests

- Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained. [*see Dosage and Administration* (2)]
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of ELOCTATE. Use Bethesda Units (BU) to report inhibitor levels.

6 ADVERSE REACTIONS

Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

6.1 Clinical Trials Experience

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

In the multi-center, prospective, open-label, clinical trial of ELOCTATE, 164 adolescent and adult, previously treated patients (PTPs, exposed to a Factor VIII containing product for ≥150 exposure days) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) received at least one dose of ELOCTATE as part of either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. A total of 146 (89%) subjects were treated for at least 26 weeks and 23 (14%) subjects were treated for at least 39 weeks.

Adverse reactions (ARs) (summarized in Table 3) were reported for nine (5.5%) subjects treated with routine prophylaxis or episodic (on-demand) therapy.

Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia. In the study, no inhibitors were detected and no events of anaphylaxis were reported.

Table 3: Adverse Reactions Reported for ELOCTATE (N=164)

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%)
General disorders and administration site conditions	Malaise Chest pain Feeling cold Feeling hot	2 (1.2) 1 (0.6) 1 (0.6) 1 (0.6)
Nervous system disorders	Dizziness Dysgeusia Headache	1 (0.6) 1 (0.6) 1 (0.6)
Musculoskeletal disorders	Arthralgia Joint swelling Myalgia	2 (1.2) 1 (0.6) 1 (0.6)
Gastrointestinal disorders	Abdominal pain, lower Abdominal pain, upper	1 (0.6) 1 (0.6)
Vascular disorders	Angiopathy* Hypertension	1 (0.6) 1 (0.6)
Cardiac disorders	Bradycardia	1 (0.6)
Injury, poisoning, and procedural complications	Procedural hypotension	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	Cough	1 (0.6)
Skin and subcutaneous tissue disorders	Rash	1 (0.6)

*Investigator term: vascular pain after injection of study drug

6.2 Immunogenicity

Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No subjects developed confirmed, neutralizing antibodies to Factor VIII. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter.

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproductive studies have not been conducted with ELOCTATE. It is not known whether or not ELOCTATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELOCTATE should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether or not ELOCTATE is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when ELOCTATE is administered to a nursing woman.

8.4 Pediatric Use

Pharmacokinetic studies in children have demonstrated a shorter half-life and lower recovery of Factor VIII compared to adults. Because clearance (based on per kg body weight) has been shown to be significantly higher in the younger, pediatric population (2 to 5 years of age), higher and/or more frequent dosing based on body weight may be needed. [*see Clinical Pharmacology* (12.3)]

Safety and efficacy studies have been performed in 56 previously treated, pediatric patients <18 years of age who received at least one dose of ELOCTATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 were enrolled in an ongoing pediatric trial. Twelve subjects (21%) were <6 years of age, 31 (55%) subjects were 6 to <12 years of age, and 13 subjects (23%) were adolescents (12 to <18 years of age). Interim pharmacokinetic data from a pediatric study of the 38 subjects <12 years of age showed that no dose adjustment had been required for patients ≥6 years old. Children age 2 to 5 years had a shorter half-life and higher clearance (adjusted for body weight); therefore, a higher dose or more frequent dosing may be needed in this age group. [*see Clinical Pharmacology* (12.3)]

8.5 Geriatric Use

Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 and over to determine whether or not they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Advise the patients to:

- Read the FDA approved patient labeling (Patient Information and Instructions for Use)
- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing.
- Report any adverse reactions or problems following ELOCTATE administration to their healthcare provider.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII therapy because this may be a sign of inhibitor development.

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ELOCTATE®
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

New Therapy Options for the Treatment of Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. It primarily affects the elderly population, is limited to the lungs, and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).[1] IPF typically presents with shortness of breath on exertion, increasing cough, bibasilar inspiratory crackles, and restrictive physiology on pulmonary function tests; clubbing of the fingers may also be seen.[1,2] It is characterized by the formation of scar tissue in the lungs in the absence of any known provocation, a variable and unpredictable natural history, acute respiratory decline, and shortened survival.[2] There have been no links to race or ethnicity leading to IPF, but there are several risk factors which have been associated with the disease. Cigarette smoking is strongly associated with the disease, along with environmental exposure to various types of dusts (brass, lead, steel, stone, animal) and abnormal gastroesophageal reflux. There is a small percentage of patients diagnosed with IPF who show a familial predisposition (5 percent of total cases). Several studies have also investigated the role of chronic viral infections — primarily Epstein-Barr and hepatitis C — as possible causes of IPF, but the link to these is tenuous at best.[1]

IPF is a rare disease affecting about 128,100 patients in the United States, with 48,000 newly diagnosed cases annually, and it leads to approximately 40,000 deaths each year in the United States.[3] It affects men at a greater rate than women (20 per 100,000 and 13 per 100,000 respectively) and has an expected median survival of three to five years from diagnosis, with respiratory failure being the most frequent cause of death.[4] The actual prevalence of IPF may be greater than reported due to a number of factors. The methods to determine prevalence often sacrifice sensitivity to improve specificity, rely on the accuracy of reporting and billing codes used by physicians, and do not always incorporate an appropriately large and diverse sample of patients.[4] The diagnosis of IPF involves a multidisciplinary discussion between pulmonologists, radiologists, and pathologists (in the case of those who do have a lung biopsy) and must carefully exclude other possible causes.[1] A complete patient history, thorough physical exam, pulmonary function assessment, chest X-rays, and high-resolution computed tomography (HRCT) images are

used in the diagnosis. A lung biopsy, typically a video-assisted thoracoscopic biopsy, is sometimes required to confirm the diagnosis.[4]

Until recently, there have been very few treatment options for IPF, and no FDA-approved medications. Previous treatments have been limited mainly to supportive measures and hence poorly effective at best. In some cases, patients under the age of 70 have been offered lung transplantation after the risks and benefits have been assessed.[2] After lung transplant, the five-year survival rate of IPF patients is estimated to be 50 to 56 percent.[1]

Current Economic Burden of IPF

As the population in the United States continues to age, both the incidence and prevalence of IPF seem to be on the rise.[5] Increasingly recognized are the serious associated co-morbidities — including pulmonary hypertension, coronary artery disease, thromboembolic disease, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, gastroesophageal reflux disease (GERD), lung cancer, and depression — that further contribute to the substantial rise in IPF-related health resource utilization (HRU).[5] This disease has often been misdiagnosed as asthma or COPD and therefore improperly and ineffectively treated with inhalers or nebulizers, leading to worse outcomes.[5]

A recent study by Collard et al was done to compare HRU and costs between patients with IPF and matched controls without IPF in U.S. Medicare recipients. An administrative claims analysis of a random 5 percent sample of Medicare beneficiaries was performed. Patients with IPF were identified based on ICD-9 codes, with at least one year of enrollment before (pre-index) and after (post-index) the first diagnosis, accounting for age, gender, race, and region. Annual HRU and medical costs (excluding outpatient drug costs) during the pre-index and post-index periods were compared between patients with IPF and matched controls. A total of 7,855 patients with IPF were matched to 38,856 controls. Compared with matched controls during the pre-index period, patients with IPF had an 82 percent higher risk of hospitalization (28.8 percent vs. 15.8 percent) and 72 percent higher total medical costs ($10,124 vs. $5,888). Compared with matched controls during the post-index period, patients with IPF had a 134 percent higher risk of hospitalization (48.7 percent vs. 20.8 percent), a similarly increased risk of emergency room visits (39.6 percent vs. 17.5 percent), and 134 percent higher total medical costs ($20,887 vs. $8,932).[6]

The authors of this study concluded that the economic burden (HRU and costs) associated with IPF in the Medicare population is substantial, and that these costs will only increase as the population of older Americans grows and as novel treatments for IPF emerge. Payors and other stakeholders in the care of patients with IPF should commit resources to understanding the care patterns that drive these increased costs and develop standard-of-care practices that provide high-quality, cost-effective care.[6] Results from this study complement a previous study performed using private, employer-based claims data that reported qualitatively similar HRU and cost for IPF patients, which further validates the findings and strengthens policy implications.[7]

Two New Novel Therapies Approved

On October 15, 2014, the U.S. Food and Drug Administration (FDA) simultaneously approved two new products for the treatment of IPF. Approvals of both Boehringer Ingel-

Table 1 Overview of Recently Approved Products to Treat IPF[8,9,17]

	Ofev	Esbriet
Manufacturer	Boehringer Ingelheim	InterMune, Inc. (part of Roche)
Class	Kinase inhibitor	Pyridone*
FDA Approved Indication	Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis
Dosing	150 mg twice daily approximately 12 hours apart, taken with food	Initiation, one capsule (267 mg) three times daily on days 1 to 7, then titrate to two capsules three times daily on days 8 to 14; Maintenance, from day 15 onward, three capsules (267 mg each) three times daily
WAC	$96,000	$93,600
For both Esbriet and Ofev, liver function tests should be performed prior to initiation of therapy, monthly for first six months, and then every three months.		

*Specific mechanism of action is unknown.

heim's Ofev® (nintedanib) and InterMune's Esbriet® (pirfenidone) were fast tracked, suggesting the FDA's recognition of the need for these medications to treat IPF, as well as a desire to level the playing field between the two manufacturers in the marketplace. "There is little to suggest that nintedanib is better or worse than pirfenidone," stated John Senior, associate director for science (hepatology) at the Center for Drug Evaluation and Research's Office of Surveillance and Epidemiology, in his consults on the nondisclosure agreements (both dated September 22, 2014), so "the careful wording of the labeling for both new agents should not confer a marketing advantage on one or the other."[16] Ofev and Esbriet have different mechanisms of action but otherwise show a fair amount of similarity.[16] Both drugs show similar efficiency versus placebo in slowing the progression of IPF, with a possible hint of improving mortality in the case of pirfenidone.[8,9] Also to be noted is the possibility of both drugs leading to mild liver injury, as well as distressing gastrointestinal effects, with Ofev causing diarrhea and Esbriet causing nausea and vomiting in a significant number of patients.[8,9] Table 1 gives an overview of the two products.

Nintedanib is a small molecule that was originally designed as an ATP-competitive inhibitor of fibroblast growth factor receptor (FGFR)-1 and vascular endothelial

Table 2 Results of Clinical Trials for Ofev[9]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ofev 150 mg twice daily vs. Placebo	Randomized, double-blind, placebo-controlled, phase 2 Patients age 40 years or older with a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for < 5 years. Patients must have had a baseline FVC ≥ 50% of predicted and a carbon monoxide diffusing capacity 30% to 79% of predicted. Patients with relevant airway obstruction or, in the opinion of the investigator, likely to receive a lung transplant during the study were excluded.	N=167 patients 52 weeks	**Primary:** Annual rate of decline in FVC **Secondary:** Time to the first acute exacerbation (investigator-reported), survival	**Primary:** The annual rate of decline in FVC was significantly improved in the Ofev group compared with placebo (-60 mL vs. -191 mL, respectively). **Secondary:** The risk of first acute IPF exacerbation was significantly reduced in patients receiving Ofev compared with placebo (Hazard Ratio: 0.16, 95% CI: 0.04 to 0.71). There was no significant difference in overall mortality been the two groups.
Ofev 150 mg twice daily vs. Placebo	Randomized, double-blind, placebo-controlled, phase 3 Patients age 40 years or older with a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for < 5 years. Patients must have had a baseline FVC ≥ 50% of predicted and a carbon monoxide diffusing capacity 30% to 79% of predicted. Patients with relevant airway obstruction or, in the opinion of the investigator, likely to receive a lung transplant during the study were excluded.	N=513 patients 52 weeks	**Primary:** Annual rate of decline in FVC **Secondary:** Time to the first acute exacerbation (adjudicated), survival	**Primary:** The annual rate of decline in FVC was significantly improved in the Ofev group compared with placebo (-115 mL vs. -240 mL, respectively). **Secondary:** The risk of first acute IPF exacerbation was not significantly reduced in patients receiving Ofev compared with placebo (Hazard Ratio: 0.55, 95% CI: 0.30 to 1.54). There was no significant difference in overall mortality been the two groups.
Ofev 150 mg twice daily vs. Placebo	Randomized, double-blind, placebo-controlled, phase 3 Patients age 40 years or older with a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for < 5 years. Patients must have had a baseline FVC ≥ 50% of predicted and a carbon monoxide diffusing capacity 30% to 79% of predicted. Patients with relevant airway obstruction or, in the opinion of the investigator, likely to receive a lung transplant during the study were excluded.	N=548 patients 52 weeks	**Primary:** Annual rate of decline in FVC **Secondary:** Time to the first acute exacerbation (adjudicated), survival	**Primary:** The annual rate of decline in FVC was significantly improved in the Ofev group compared to placebo (-114 mL vs. -207 mL, respectively). **Secondary:** The risk of first acute IPF exacerbation was significantly reduced in patients receiving Ofev compared with placebo (Hazard Ratio: 0.20, 95% CI: 0.07 to 0.56). There was no significant difference in overall mortality been the two groups.

growth factor receptor (VEGFR)-2. Both of these receptors are proangiogenic receptor tyrosine kinases and nintedanib was designed as an antiangiogenic drug for cancer treatment. In two phase 3 INPULSIS® studies, nintedanib was shown to slow disease progression in patients with IPF by reducing the annual rate of decline in forced vital capacity (FVC), probably through its antifibrotic and anti-inflammatory properties (Table 2).[9]

The recommended daily dosing of nintedanib is 150 mg twice daily taken with food.[9] Dosing adjustments or temporary interruption may be recommended in the case of certain adverse reactions. In the clinical trials, nintedanib was associated with an increase in liver enzymes (AST, ALT, ALKP, GGP) in a small percentage of cases; however, each case was reversible with dose adjustment or interruption and none were associated with sustained liver injury.[9] Other common side effects associated with nintedanib include diarrhea, nausea, and vomiting. Diarrhea tended to be the most frequently experienced adverse event, occurring in 61.5 percent of patients versus 18.6 percent in the placebo group; this led to a permanent dose reduction in 11 percent of patients, while 5 percent of patients discontinued use.[9]

In both of the INPULSIS trials, nintedanib significantly reduced the rate of decline in FVC over the 52-week treatment period, which is consistent with slowing of disease progression.[11] The annual wholesale acquisition cost (WAC) associated with Ofev is $96,000.[17]

Pirfenidone is a small, orally available molecule that demonstrates anti-inflammatory and antifibrotic effects. In the phase 3 multinational studies CAPACITY and ASCEND, pirfenidone treatment reduced lung function decline, improved progression-free survival, and reduced both all-cause mortality as well as treatment-emergent IPF-related mortality at one year, as compared with placebo (Table 3).[10] There is no mortality claim on the FDA-authorized labeling of the drug since the FDA scrutinized mortality for the full period of the ASCEND and prior CAPACITY studies, which included follow-up survival data beyond 72 weeks. The apparent mortality benefit appeared to dissipate beyond 52 weeks, but this could also be a function of significantly fewer evaluable patients beyond this time frame.

After a 14-day titration, the recommended daily maintenance dosage of pirfenidone is 801 mg (three 267 mg capsules) three times a day with food, for a total of 2,403 mg/day taken

Table 3 Results of Clinical Trials for Esbriet[8]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Esbriet 2,403 mg/day vs. Placebo	Multicenter, randomized, double-blind, placebo-controlled Adults who had a clinical and radiographic diagnosis of IPF and who had a percent predicted forced vital capacity (%FVC) ≥ 50% at baseline and a percent predicted diffusing capacity of the lungs for carbon monoxide ≥ 30%	N=555 patients 52 weeks	**Primary:** The change in %FVC	**Primary:** The change in %FVC demonstrated a statistically significant treatment effect of Esbriet compared with placebo. The mean change in FVC from baseline was -235 mL in the Esbriet group compared with -428 in the placebo group.
Esbriet 2,403 mg/day vs. Esbriet 1,197 mg/day vs. Placebo	Multicenter, randomized, double-blind, placebo-controlled Adults who had a clinical and radiographic diagnosis of IPF and who had a %FVC ≥ 50% at baseline and a percent predicted diffusing capacity of the lungs for carbon monoxide ≥ 35%	N=435 patients 72 weeks	**Primary:** The change in %FVC	**Primary:** The change in %FVC demonstrated a statistically significant treatment effect of Esbriet compared with placebo. The mean treatment difference in change in FVC between the Esbriet 2,403 mg group and placebo was 157 mL.
Esbriet 2,403 mg/day vs. Placebo	Multicenter, randomized, double-blind, placebo-controlled Adults who had a clinical and radiographic diagnosis of IPF and who had a %FVC ≥ 50% at baseline and a percent predicted diffusing capacity of the lungs for carbon monoxide ≥ 35%	N=344 patients 72 weeks	**Primary:** The change in %FVC	**Primary:** The change in %FVC did not demonstrate a statistically significant treatment effect of Esbriet compared with placebo.

at the same time each day.[8] Elevated liver enzymes (AST, ALT, bilirubin) have been associated with pirfenidone and may require a temporary dose reduction or discontinuation if not resolved. At the recommended dosage of 2,403 mg/day, 14.6 percent of patients on pirfenidone (compared with 9.6 percent on placebo) permanently discontinued treatment because of an adverse event. The most common adverse reactions leading to discontinuation were rash and nausea, and the most common reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.[10] Pirfenidone, as compared with placebo, reduced the relative risk of death or disease progression by 43 percent (CI = 95 percent; $p < 0.001$).[10] Treatment with pirfenidone was found to be generally safe, had an acceptable side effect profile, and was associated with fewer deaths than placebo.[10] The annual WAC associated with Esbriet is $93,600.[17]

Implications for Managed Care

Prior to the approval of Esbriet and Ofev, treatment options for IPF were extremely limited, and there were no FDA-approved medications. With these recent approvals, there is a new focus on improving survival and enhancing the quality of life of patients diagnosed with IPF.

Both Ofev and Esbriet have shown efficacy in slowing the annual decline in lung function in similar patient populations. However, there have been no comparative studies between the two. There was no statistical difference in all-cause mortality between Esbriet or Ofev compared to placebo in any of the phase 3 clinical trials (according to FDA analysis).[8,9]

Through better education and earlier diagnosis, there is significant opportunity to improve the overall quality of life for these patients, have better overall outcomes, and also to achieve tremendous cost benefits. Esbriet and Ofev offer much-needed treatment options for IPF patients, but at a significant cost to payors ($93,600 and $96,000 WAC, respectively).[17] In addition to the high cost of medication, another challenge that these patients face is accessibility to these medications, as they are often required to use specialty or mail-order pharmacies by the payors.[12] There are patient-assistance programs available for each of these medications, through the manufacturers as well as private sources, which may help certain patients gain access to medications they otherwise might not be able to afford.[12-15]

At this time, due to the difficulty of treating this disease and the high costs associated with therapy, it is imperative that health plans and providers work together to ensure that patients are receiving the support and treatment that they require and ultimately attain the best possible outcomes. Both these drugs represent a good start in the treatment of patients with IPF, but there is still a significant amount of work that needs to be done to impact this underappreciated, but potentially deadly disorder.

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At the end of the day, relying on cost for your formulary decisions is not enough.

Indications and Usage

- Victoza® (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

- Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk.
- Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.
- Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of Victoza® and prandial insulin has not been studied.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

- **Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.**
- **Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Victoza® and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Victoza®.**

Contraindications

- Victoza® is contraindicated in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

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[a]Intended for members of formulary committees pursuant to section 114 of the FDA Modernization Act (section 502(a) of the Food, Drug, and Cosmetic Act).

Warnings and Precautions

- **Pancreatitis: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.**
- **Never Share a Victoza® Pen Between Patients, even if the needle is changed.** Pen-sharing poses a risk for transmission of blood-borne pathogens.
- **Use with Medications Known to Cause Hypoglycemia:** When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin, serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
- **Renal Impairment:** Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported postmarketing. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.
- **Macrovascular Outcomes:** There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

Adverse Reactions

- The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, dyspepsia, constipation, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Use in Specific Populations

- Victoza® has not been studied in patients with type 2 diabetes below 18 years of age and is not recommended for use in pediatric patients.
- There is limited data in patients with renal or hepatic impairment.

Please see brief summary of Prescribing Information on next pages.

1214-00024713-1

April 2015

VICTOZA®
liraglutide (rDNA origin) injection

Victoza® (liraglutide [rDNA origin] injection)
Rx Only
BRIEF SUMMARY: Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions]*. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Victoza® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Victoza® *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk *[see Warnings and Precautions]*. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and prandial insulin has not been studied.

CONTRAINDICATIONS: Victoza® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Victoza® is contraindicated in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with Victoza® have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and Victoza® use in humans. Victoza® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Victoza® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Victoza®. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. **Pancreatitis: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. **Never Share a Victoza® Pen Between Patients:** Victoza® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Adverse Reactions]*. **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors *[see Warnings and Precautions];* Pancreatitis *[see Warnings and Precautions];* Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions];* Renal Impairment *[see Warnings and Precautions];* Hypersensitivity Reactions *[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 Victoza® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Reaction	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Reaction	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4

Add-on to Metformin + Rosiglitazone		
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175
Adverse Reaction	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Headache	8.2	4.6
Constipation	5.1	1.1

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

Immunogenicity: Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In the five double-blind clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five double-blind clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia:* In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self–treat	0.1 (0.001)	0	0
Patient able to self–treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self–treat	0.1 (0.003)	0	0
Patient able to self–treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self–treat	0	—	0
Patient able to self–treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self–treat	2.2 (0.06)	0	0
Patient able to self–treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** *Bilirubin:* In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. *Calcitonin:* Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established *[see Warnings and Precautions]*. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Medullary thyroid carcinoma *[see Warnings and Precautions];* Dehydration resulting from nausea, vomiting and diarrhea *[see Warnings and Precautions];* Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions];* Angioedema and anaphylactic reactions *[see Contraindications, Warnings and Precautions];* Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Warnings and Precautions]*.

OVERDOSAGE: Overdoses have been reported in clinical trials and post-marketing use of Victoza®. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

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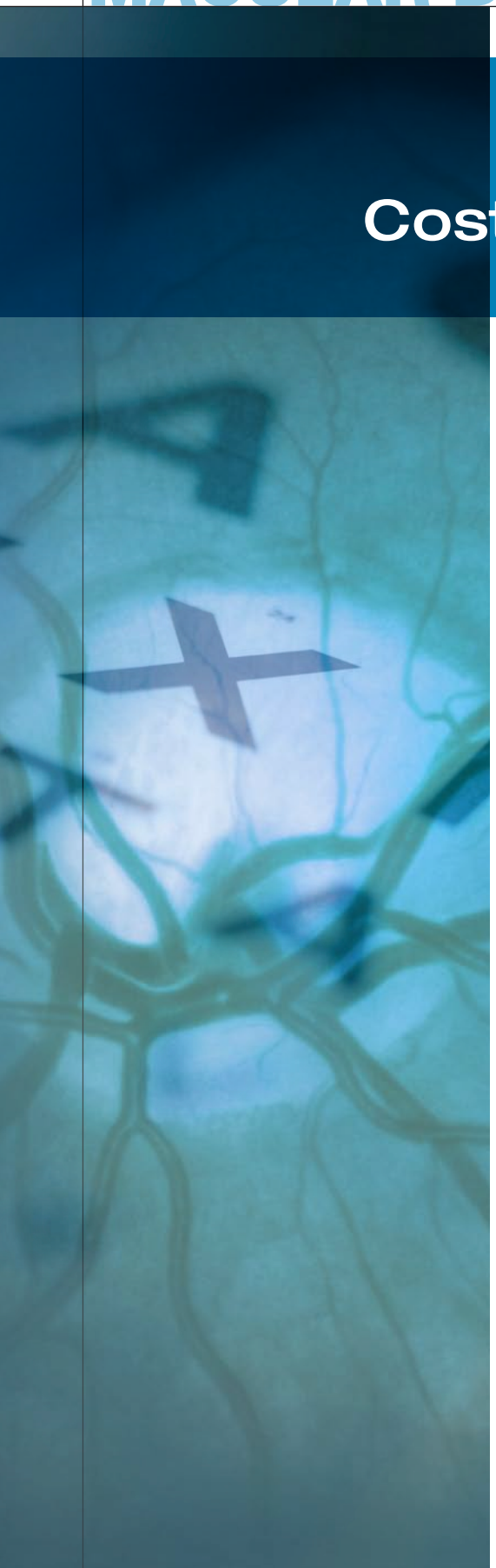
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection



Evaluating AMD for Cost Savings Opportunities

Age-related macular degeneration (AMD) is a degenerative eye disease that affects an estimated 15 million people in the United States.[1] AMD is the leading cause of blindness and central vision loss among adults over 65 years old, and progresses with age. It affects 14 to 24 percent of the U.S. population between ages 65 and 74, and 35 to 40 percent of people age 74 or older; this translates to more than one in three persons developing signs of AMD, with more than 200,000 new cases diagnosed each year.[2]

There are two primary types of AMD, both of which result in dysfunction of the retina and eventual central vision loss. Dry, or atrophic, AMD is characterized by hard yellow deposits called drusen, which form on and around the macula. This is part of the normal aging process, and the majority of people over age 55 will have drusen with no negative effects. In some cases when the drusen are large and numerous, damage to the macula can occur resulting in central vision loss. In about 10 percent of cases, dry AMD will progress to the more advanced and damaging form of AMD described as wet, neovascular, or exudative AMD. Wet AMD is caused by the proliferation of abnormal blood vessels in the retina stimulated by vascular endothelial growth factor (VEGF). These vessels leak blood and protein into the retina which eventually causes irreversible damage to the photoreceptors and results in rapid vision loss if left untreated.

Early detection of AMD is essential for effective treatment. Many patients who have had the disease undiagnosed for many years may notice changes in vision which are symptomatic of both dry and wet AMD. Dry AMD symptoms consist of the need for brighter light when reading, difficulty adapting to low-light levels, increased blurriness of printed words, decreased vision with brightness of colors, blurred spot in the center of the field of vision, and/or a blank or black spot in the field of vision in which the spot will begin to grow over time possibly leading to blindness. The symptoms of wet AMD consist of an abrupt decline in central vision, visual distortions, and a well-defined blind spot positioned in the center of vision. Although AMD can be a debilitating condition, many patients do have the ability to live healthy and independent lives. It is crucial that patients are educated about the disease and work with retina specialists to devise treatment plans.

Magellan Rx Management has partnered with major health plans across the country to provide a fair and equitable margin for the use of bevacizumab for retina diseases when clinically appropriate.

Current Available Treatments

Dry AMD develops more gradually, and the National Eye Institute recommends supplementation of antioxidants, lutein and zeaxanthin to slow progression, with the potential to improve visual acuity in some patients.[3] In May 2013, the National Eye Institute conducted a study, Age-Related Eye Disease Study 2 (AREDS2), in order to see whether modifications could be made to the original AREDS formulation. The AREDS2 formulation now consists of 500 mg of vitamin C, 400 IU of vitamin E, 80 mg zinc, 2 mg copper, 10 mg lutein, and 2 mg zeaxanthin.[3]

Wet AMD is more progressive, and patients usually need treatment soon after symptoms appear. New drugs, called anti-vascular endothelial growth factor (Anti-VEGF) injections, promote regression of the abnormal blood cells that develop during wet AMD, helping to improve vision. Macugen® (pegaptanib), Lucentis® (ranibizumab), Eylea® (aflibercept), and Avastin® (bevacizumab) are used in the treatment of wet AMD (Table 1).[4]

When Macugen was first approved, one study had found 70 percent of patients stabilized with no further visual loss.[5] Macugen has not been found to improve vision. Lucentis improved upon the results of the Macugen study; it was found that 95 percent of patients treated with Lucentis retained their vision, and approximately 40 percent of patients who completed one year of treatment improved their vision to 20/40 or better.[6] Eylea was approved based on the results of two phase 3 clinical trials. These trials proved that Eylea, injected every eight weeks following an initial loading dose of three monthly injections, was clinically equivalent to Lucentis, injected every four weeks, as measured by the primary end point of maintenance of visual acuity, less than 15 letters of vision loss on an eye chart over the course of 52 weeks.[7] In the Comparison of AMD Treatment Trials (CATT), a two-year trial in which Avastin (bevacizumab) and Lucentis (ranibizumab) treatment schedules were compared, it was shown that bevacizumab and ranibizumab had similar beneficial effects on visual acuity. At the conclusion of the study, it was found the average gains in visual acuity between both drugs were within 1.4 letters, and approximately 60 percent of all patients had 20/40 vision or better.[8]

In a study comparing Lucentis and bevacizumab, researchers analyzed insurance claims data for 58,612 patients who received more than 380,000 injections of the two drugs. They found that both posed low risks of infection.[9] Lucentis costs approximately $2,000 per dose and comes in ready-to-use vials from the manufacturer,

Table 1 Available Treatments for AMD[4]

Brand	Generic	Dose and Frequency (AMD)	Cost/Dose (ASP*** + 6%)	Annual Cost/Eye
Avastin	bevacizumab	1.25 mg monthly	$69.60**	$835.20
Eylea	aflibercept	2 mg every eight weeks*	$1,961.00	$13,727.00
Lucentis	ranibizumab	0.5 mg monthly	$1,957.05	$23,484.60
Macugen	pegaptanib	0.3 mg every six weeks	$1,031.85	$9,286.65

*After loading dose schedule is completed, 2 mg every 4 weeks x 3 doses **J9035 ***ASO 10/1/15 rates

while bevacizumab costs approximately $70 per dose and is packaged in much larger vials intended for cancer treatment and must be compounded into smaller doses for treatment of wet AMD. Studies indicate that the two drugs are equally effective in treating wet AMD.[9] Another study found bevacizumab is not linked to a higher risk of an eye infection called endophthalmitis, versus those patients treated with Lucentis. Researchers analyzed more than 296,000 injections of bevacizumab and more than 87,000 injections of Lucentis, and found that the rates of serious eye infection were 0.017 percent for bevacizumab and 0.025 percent for Lucentis.[9]

Management Approaches for Anti-VEGF Intravitreal Injections

Magellan Rx Management has a clinical program underway to help manage the treatment of neovascular AMD. An analysis of payor claims from calendar year 2013 showed that bevacizumab is utilized in the treatment for the majority of Medicare AMD patients.[4] The per-member per-month (PMPM) for this population for bevacizumab was $0.20, which is significantly lower than that of Lucentis and Eylea, which were $3.08 and $0.78 respectively.[4] This dynamic might be driven by benefit design as Medicare beneficiaries typically had a 20 percent coinsurance for medical benefit drugs. For the commercial population, the PMPM for bevacizumab was $0.01, which is significantly lower than that of Lucentis and Eylea, which were $0.26 and $0.11 respectively.[4] Even though bevacizumab is used off-label and has to be compounded, it is used by more than 60 percent of the Medicare population for retina diseases.

Reimbursement strategies and network engagement are essential for successful management of this category. With conventional, ASP-based pricing, providers are discouraged from using cost-effective pharmaceutical alternatives like bevacizumab due to the decreased margin realized for the practice. Magellan Rx Management has partnered with major health plans across the country to provide a fair and equitable margin for the use of bevacizumab for retina diseases when clinically appropriate. The goal is to ensure that the use of this product is not disincentivized, allowing providers to choose medications without fear of losing reimbursement.

To drive success of this initiative, engagement with the provider network is crucial. Provider notification and education are keys to changing specialist prescribing patterns. Identification and monitoring of participating practices through analysis of claims information is important to track progress. Both prescribers and their billing teams should be educated on the reimbursement changes and proper billing practices. Once all key stakeholders are informed and aligned, favorable results occur for all parties: Members receive clinically effective and appropriate care at potentially reduced out-of-pocket expense, practices have lower carrying costs and improved reimbursement, and payors have reduced drug expenditures for the treatment of retina diseases.

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Accountable Care Organizations: What Can We Learn from Our Experience?

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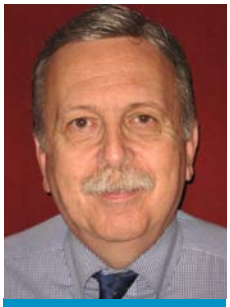


William J. Cardarelli, PharmD

Accountable Care Organizations (ACOs) have become a familiar part of today's health care landscape. ACOs, which were created under the Affordable Care Act (ACA), are comprised of groups of physicians, hospitals, and other health care providers with the objective to provide quality care and reduce unnecessary costs to patients and the health care system. ACOs were put into place in order to align incentives with Health Care Reform in the delivery of better population health, improved patient satisfaction, and the reduction in health care spending. As these organizations become increasingly prevalent, the availability of data collected over the past several years offers an opportunity to review the experiences, challenges, and successes of ACOs.

Background

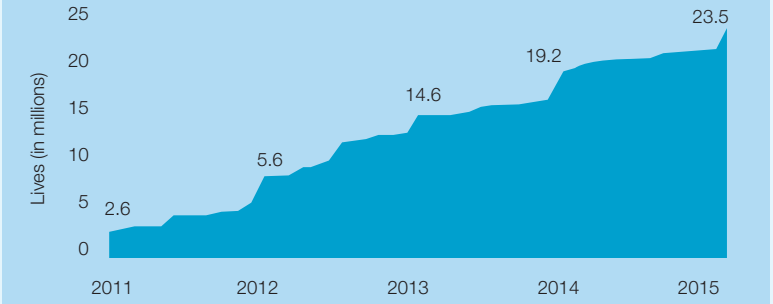
The ACA authorized the Centers for Medicare & Medicaid Services (CMS) to establish the Medicare Shared Savings Program.[1] This program assists Medicare fee-for-service (FFS) providers in becoming part of an ACO and is intended to move health care delivery away from an FFS model, with the goal of provider reimbursement being dependent on value-based patient care. Since the establishment of the first ACOs as part of the Shared Savings Program, additional ACOs have been created under the umbrella of the Pioneer ACO Model, which included 32 original participants and decreased to 18 participants as of April 30, 2015.[2] The Pioneer Model was intended to establish a core of early adopters to test the clinical and economic outcomes associated with ACOs. Although this specific program is no longer accepting new applicants, the Shared Savings Program continues to enroll ACOs. As of January 2015, there were 404 Shared Savings Programs serving 7.3 million assigned beneficiaries.[3]

In May 2011, CMS announced the Advance Payment Model, which is designed for physician-based and rural providers who come together to coordinate care for Medicare patients, an initiative with 35 participants.[3] Through this program, participants receive an advance on the shared savings they are expected to earn to help fund the required startup costs necessary to improve care coordination.

Figure 1: Total Public and Private Accountable Care Organizations, January 2011 to January 2015

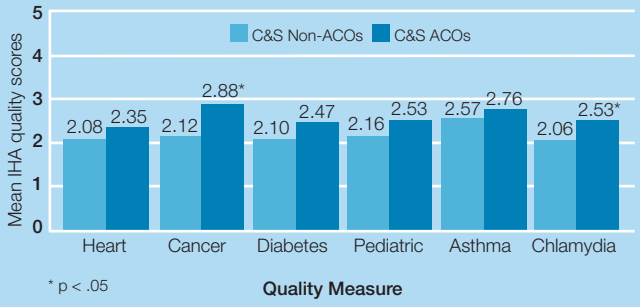
Source: Leavitt Partners Center for Accountable Care Intelligence[1]

Figure 2: Number of ACO Covered Lives, January 2011 to January 2015



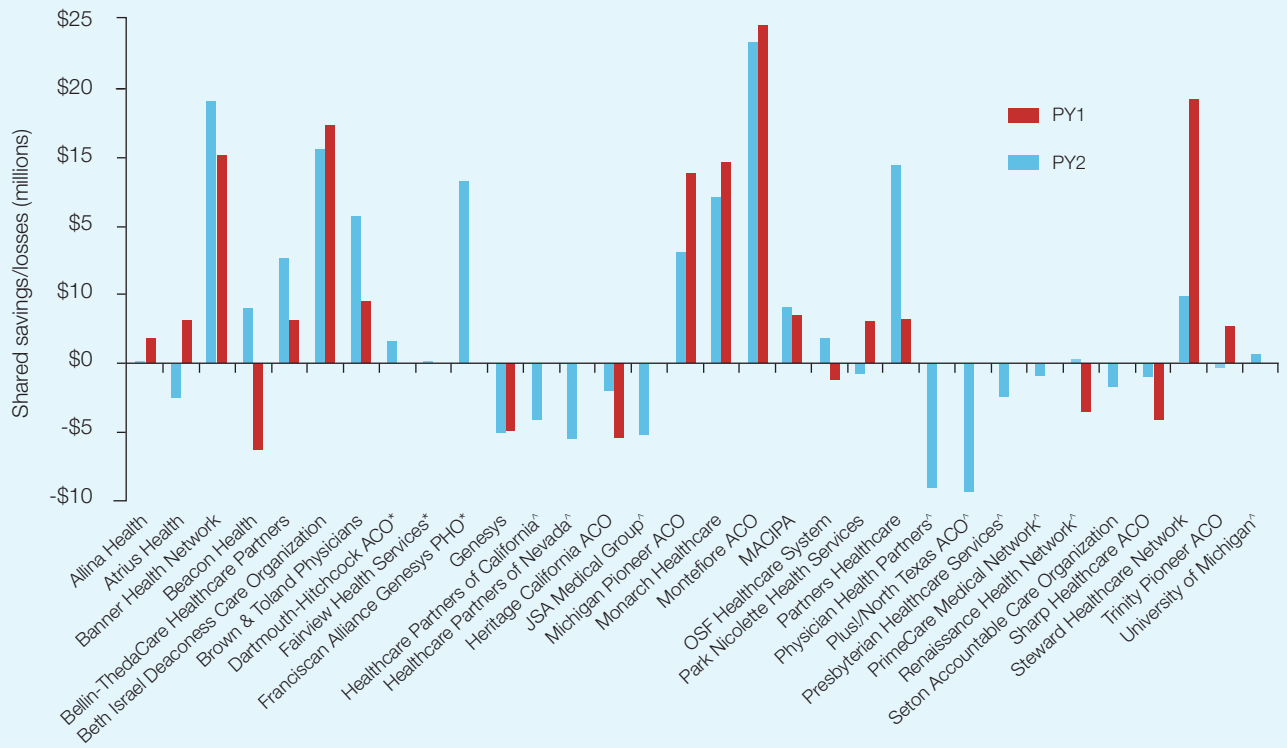
Source: Leavitt Partners Center for Accountable Care Intelligence[1]

Figure 3: Mean Quality Scores for California Medical Groups, Excluding Kaiser Permanente FY 2013[5]



Cattaneo and Stroud (C&S) survey of California ACOs and Non-ACOs
Source: Author's calculations based on data from the Integrated Healthcare Association

Figure 4: Pioneer ACO Gross Savings/Losses, Performance Year 1 vs. Performance Year 2[7]



*Deferred reconciliation until after Performance Year 3
^Left the Pioneer Program after Performance Year 1

Source: The Brookings Institution

Growth and Changes in the ACO Arena

Among the most significant trends regarding ACOs is the steady increase in the number of new organizations since 2011, when there were fewer than 100 ACOs nationwide. Since, there has been a sevenfold increase in the number of ACOs, and nearly a tenfold increase in the number of ACO covered lives, surging from 2.6 million lives in 2011 to 23.5 million lives in early 2015.[1] From the perspective of access to an ACO, it is reported that in 2014, nearly 70 percent of the U.S. population lived in areas served by at least one ACO and 44 percent of Americans resided in areas served by at least two ACOs.[4] In certain geographies, California for example, the expansion has been even more rapid, with a reported increase of 78 percent in the number of lives covered by ACOs from 2012-2014, jumping from 514,000 to 915,000 ACO-covered lives.[5]

Improving the Quality of Care

ACO performance is assessed by quality metrics, which, for the Shared Savings Programs, consist of 33 measures across four quality domains. Each represents 25 percent of an ACO's score[6]:

1. Patient/caregiver experience
2. Care coordination/patient safety
3. Preventive health
4. Clinical care for at-risk populations (diabetes, depression, hypertension, heart failure, coronary artery disease, and ischemic vascular disease)

As ACOs become more experienced with coordinating patient care, overall improvements in quality measures are being observed. Theoretically, this trend suggests an overall improvement in patient care among high-performing ACOs.

The ACO model is constantly evolving as health care providers and CMS get more experience with coordinated care and new payment schemes. Part of this evolution includes introducing new models that address unmet needs of current ACOs.

While the data for the Pioneer Model and the Shared Savings Program is compiled nationally, more specific trends can be seen regionally. The University of California, Berkeley assembled data from a panel of health plans that are part of ACOs in the area. Figure 3 shows the quality scores for asthma care, cancer screening, chlamydia screening, diabetes care, heart care and pediatric care. The results were assessed relative to other non-ACO medical practices. Taking into account results from other quality domains, the Berkeley evaluation determined that, overall, ACOs provide at least equivalent and on a few measures, better quality of care than other delivery models in the state. This research demonstrated the California ACOs, included in the evaluation, achieved slightly better patient experience scores than non-ACOs.[5]

The Berkeley evaluation of Pioneer ACOs also showed an improvement in care. The 23 ACOs that remained in the Pioneer Model showed an overall improvement in average quality scores between the first (2012) and second (2013) performance years. Quality Domain 4, At Risk Populations, had the greatest improvement in year two, demonstrating an increase from a score of 67.5 percent to 83 percent.[7] These improvements suggest ACOs are getting better at coordinating care for patients in high-risk populations.

An assessment of ACOs in Michigan also demonstrated positive results with improvements in 28 of 33 measures — including depression screening, medication reconciliation, colorectal cancer screening, and normalizing blood-sugar levels.[8]

The demonstration of cost-savings was a meaningful goal of the ACO initiative. In 2012, CMS projected that ACOs would save $1 billion in the first three years of the program and as much as $5 billion by 2019.[1] While financial results for 2014 are not yet available, it appears as though ACO savings are ahead of these projections. According to CMS, in FY 2013, ACOs in the Pioneer Model generated savings of more than $96 million.[9] ACOs belonging to the Shared Savings Model generated $383 million in shared savings in the same year.[9] ACOs that are generating cost-savings while meeting quality metrics are eligible to keep a portion of the funds. For example, Illinois-based Heartland Regional Medical Center joined the Shared Savings Program in 2012 and was awarded $2.9 million in the first year for its cost-savings efforts.[10] This reflects about 60 percent of the total Medicare savings that were derived from the organization's quality and cost-control strategies.[10] Most ACOs, however, do not experience such success in their first years. In fact, it has been reported that three out of four ACO program participants did not meet their cost-savings goal within the first year of implementation.[10] Although, as the U.S. health care system grows in ACO experience, common strategies have been identified that are more likely to achieve cost-savings and better quality of care.

Factors for ACO Success/Challenges

The early adopters of the ACO model were physician offices and hospitals that were previously successful with coordination of care. However, not all facilities, especially independent physician offices and hospitals, were eager to participate. The resistance to ACO participation often centered on common challenges, one of the most significant being the cost and effort associated with transitioning to an electronic health record (EHR) system. Additionally, since the ACO model requires all of the participating facilities to pool risk, previously successful practices resisted joining. However, for those organizations that have participated, their success has been attributed to the following factors:

• **Size/scale:** A population of at least 10,000 lives is required in order to overcome the startup costs for components such as EHRs.
• **Care management:** The use of care analytics assists with the identification of high-risk patients and with the utilization of appropriate care transition programs, helping to reduce avoidable readmissions.
• **Electronic health records:** Facilitates the success of ACOs by streamlining the administration and sharing of relevant patient information, giving both patients and providers timely and organized access to health information that is used to support the making of health care decisions.
• **Effective partnerships:** Forming new partnerships between medical groups/hospitals and community health organizations (mental health, home health, skilled nursing facilities) supports the success of ACOs. Establishing shared goals and uniform policies wherever possible improves the knowledge and communication among the ACO stakeholders.

ACO Innovations

The ACO model is constantly evolving as health care providers and CMS get more experience with coordinated care and new payment schemes. Part of this evolution includes introducing new models that address unmet needs of current ACOs. Recently CMS has introduced the Next Generation ACO Model, a new model that represents a higher associated financial risk and higher reward than either the Pioneer Model or Shared Savings Program.[11]

This new model would be targeted toward ACOs more experienced in care coordination. The goal of this model is to test whether strong financial incentives for ACOs, coupled with better tools to support patient engagement and care management, can improve health outcomes and lower expenditures for Medicare beneficiaries.[11] Unlike previous models, ACOs participating in the Next Generation Model will have their quality metrics and patient experience ratings published on the CMS website. Enrollment in this program ended June 2015, and the program is expected to last up to five years.[11]

Conclusions

While the jury is still out on how the introduction of ACOs has shaped patient care in the United States, the cost-savings, quality improvement, and expansion are promising signs. Going forward, the size and scope of ACOs may continue to expand as participation starts to offer better incentives to providers. Although ACOs are just one of many programs put into place by the ACA to help curb health care spending, the resulting integration of resources, interdisciplinary coordination, and quality improvements will hopefully have a dramatic impact on the future of health care delivery.

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Clinical Programs Designed to Improve Star Ratings

The Centers for Medicare & Medicaid Services (CMS) began measuring Star Ratings in 2007 for Medicare Part D and added Medicare Advantage (Part C) in 2008. This scoring system grades Medicare health plans based on the quality of their member services. The goal of this rating system is to incentivize health plans to provide higher overall quality of care to Medicare beneficiaries. In fact, it has been estimated that every one-star improvement in an overall Star Rating results in an incremental bonus payment as high as $50 per-member per-month (PMPM). This represents a substantial opportunity for Medicare plans that can deliver high-quality care to their beneficiaries.

In recent years, various clinical programs have been developed and implemented to aid in the achievement of better compliance with measures and higher Star Ratings. Magellan Rx Management has been at the forefront of developing and implementing some of these clinical programs. These programs are designed to specifically address the quality standards incorporated into the CMS Star Rating measures. The results of two of these programs were recently presented at the Academy of Managed Care Pharmacy's 27th Annual Meeting & Expo.

Diabetes Management

The first of the two clinical programs focused on the Diabetes Treatment measure, which looks at the appropriate utilization of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or direct renin inhibitors (ACE/ARBs) in patients with diabetes and hypertension. Health plan members are incorporated into this measure when they have a pharmacy claim for both a diabetes and hypertension medication. Compliance with the measure is based on the percentage of patients with a claim for an antidiabetic agent and a claim for an antihypertensive agent who have filed a claim for an ACE/ARB.

Between January and December 2014, Magellan Rx Management implemented a PharmD-led telephonic outreach program intended to improve compliance with the Diabetes Treatment measurement. Through partnership with a regional health plan, a total of 4,185 members were identified with concomitant claims for both antidiabetic and antihypertensive products. Of these members, 903 were identified as noncompliant cases. Clinical staff members from Magellan Rx Management then contacted providers, pharmacies, and patients on behalf of the health plan to increase treatment rates where appropriate.

Outreach to providers consisted of confirming diagnoses, obtaining any contraindications to ACE/ARB therapy, and — where appropriate — recommending evaluation for ACE/ARB therapy. Patients would then be contacted for educational purposes, including consultation regarding their diabetes and hypertension. The

conversation would then lead to a dialogue surrounding why therapy with an ACE/ARB would likely be beneficial for the patient. The callers would then conclude their outreach by encouraging the patient to further discuss the addition of an ACE/ARB to their regimen at their next office visit.

Without successful conversions from noncompliant to compliant, the treatment rate would have been as low as 75.3 percent, resulting in a 1-star rating for the Diabetes Treatment measure. The incorporation of targeted telephonic patient education and clinical recommendations to pharmacies and providers produced an 88.1 percent treatment rate, resulting in a 4-star rating for this specific measure.

The national average for improvement in treatment rates in a health plan utilizing a Diabetes Treatment clinical program was 0.8 percent from 2013 to 2014. This particular clinical telephonic outreach program resulted in a 4.5 percent increase during that same time period. This represented a 1-star improvement (and prevention of a 2-star decrease) from the previous year.

Had this measure not been retired by CMS, Magellan Rx Management would have continued outreach in subsequent years. However, measure D10, Diabetes Treatment, was retired in early 2015. This will likely be replaced by a measure aimed at statin utilization based on updated guidelines released by the American College of Cardiology/American Heart Association (ACC/AHA). The measure, Statin Use in Persons with Diabetes, suggests utilization of a statin for primary cardiovascular event prevention in patients aged 40 to 75 years old with a diagnosis of diabetes. This is a display measure for 2015 and may potentially become part of Star Ratings for 2017.

Rheumatoid Arthritis

Magellan Rx Management also designed and implemented a similar program geared towards measure C19, Rheumatoid Arthritis (RA) Management. This population consists of all members with two or more outpatient (or nonacute inpatient) visits with a diagnosis of RA. Compliance with the measure is achieved once the member has a pharmacy or medical claim for a disease-modifying antirheumatic drug (DMARD). In addition to processing a claim for a DMARD, correction of inappropriate billing for RA improves compliance by removing the member from the measurement population.

Between January and December 2014, Magellan Rx Management implemented a clinical program similar to the program designed to improve measure D10. This PharmD-led telephonic clinical program identified 568 members of a regional health plan with at least two medical claims with an RA diagnosis. Of these members, 325 were identified as noncompliant cases.

Outreach began by targeting the provider offices billing for an RA diagnosis. If inappropriately billed (i.e., patient does not have RA but has OA), correct billing codes were provided to the office and necessary updates were made. Once the inappropriate diagnosis code was removed from the medical claims, the patient would then be removed from the measurement population. Once the diagnosis was confirmed, clinical staff members would provide rationale for DMARD use in patients with RA and collect contraindications to usage for individuals unable to receive a DMARD.

Following the clinical discussion with the provider's office, pharmacists reached out to the patient. During patient outreach, callers would guide the discussion topics to obtain a sense of RA disease control and symptom severity, educate regarding the benefits of DMARD therapy, and assess receptivity toward initiating a DMARD.

After the patient had a chance to meet with his or her provider, a follow-up call to the provider would occur. During that call, information would be requested regarding the status of DMARD prescribing (if this was done), and additional follow-up would be completed to ensure the prescription was picked up. Lastly, patients would then be offered the opportunity to speak with a pharmacist regarding the details of their new prescription.

Through advanced analytics and clinical outreach, the RA management program resulted in a treatment rate of 88.1 percent (a 5-star rating), representing an 8.7 percent increase compared to the same time period in 2013. This increase included 71 patients initiated on a DMARD and 55 patients removed from the measurement (due to corrections of inappropriate RA diagnosis), as a result of clinical outreach. Without this intervention, the treatment rate would have been as low as 63.2 percent, resulting in a 2-star rating. Based on the initial success of this program, the clinical intervention was continued for 2015. The preliminary 2015 results show a treatment rate well within the range of a 5-star rating.

The results from these clinical programs highlight the ability of targeted clinical interventions to improve CMS Star Ratings. Additionally, proactively identifying potentially noncompliant members and conducting the appropriate outreach to physicians, pharmacies, and patients can improve quality of care for Medicare beneficiaries.

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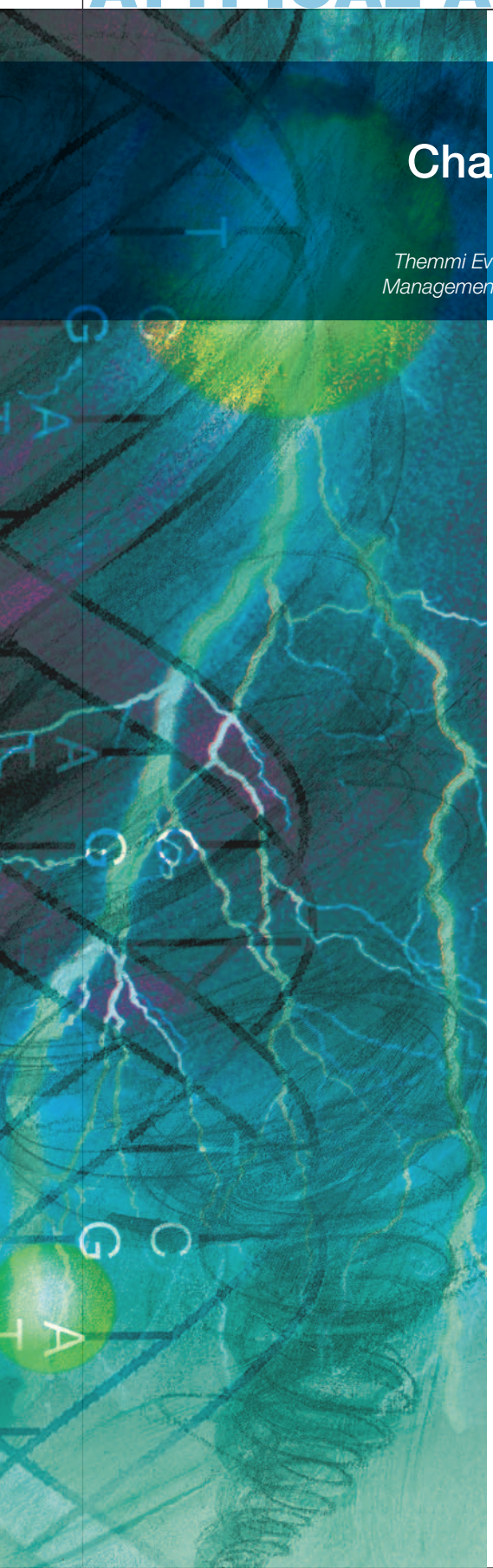

Atypical Antipsychotics: Challenges of Formulary Management in Patients with Serious Mental Illness

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Health plans and pharmacy benefit managers (PBMs) commonly utilize restrictive formulary strategies to manage pharmacy expenditures by implementing techniques that promote cost-effective use of generic and preferred branded medications. Typically, these cost-containment strategies have focused on therapeutic categories associated with high costs to the health plans. Many payors have applied this approach to managing the utilization of atypical antipsychotics. However, successfully managing this class may not be as simple as utilizing a restricted formulary. For the vulnerable member population, especially in patients with serious mental illness, it is imperative to manage availability of medications, address patient and prescriber preferences, and be fiscally responsible, all while employing a comprehensive approach to care. It is critical to find a balance that provides suitable medication access to the appropriate patient population by carefully evaluating the patient's clinical situation in order to optimize treatment.

Step therapy and prior authorization policies are two strategies that have been effective for managing pharmacy formularies for many therapeutic categories.[1,2] However, these policies may not be ideal approaches for all disease states and therapeutic categories. Patients with serious mental illness may be vulnerable to adverse consequences of restrictions due to the complexity of this patient population and the integral role these medications play, along with psychosocial and cognitive therapies, in the treatment of severe mental illnesses. Huskamp et al suggest formulary restriction of antipsychotics should be undertaken with caution.[3] Most importantly, changes in formulary design should aim to avoid negative impact on compliance with therapy. Untreated and/or nonadherent patients may be at increased risk for psychiatric episodes, complications, or hospitalization, resulting in rising medical costs and possibly the inability to work or function socially.

For example, schizophrenia and bipolar disorder are two severe mental illnesses affecting a large proportion of the U.S. population. For decades, antipsychotics have been used to help treat both conditions. While widely used, atypical antipsychotics — including both oral and injectable long-acting agents — are generally more expensive than traditional antipsychotic agents. These

therapies may be listed as among the top drugs by annual expenditure for health plans, prompting formulary management of their use to arise as a priority.[4] As the majority of oral atypical antipsychotics are now available as generic formulations, some payors have re-evaluated their formularies, driving generic utilization in an effort to realize cost-savings.

Product selection is important among these therapies. Not only must the therapy match the patient's clinical and lifestyle needs in a manner that promotes adherence, caution must be taken with regard to considering underlying conditions, side effects, and potential adverse reactions. For example, many of the older atypical antipsychotics, some of which are potentially cost-effective based on generic availability, have been associated with increased risk of hyperglycemia and diabetes, a condition whose incidence is of growing concern in the United States. This is an important factor in the selection of a therapeutic agent. Newer atypical antipsychotics with a relatively neutral profile may prove more appropriate for some patients, such as those for whom hyperglycemia and diabetes are a concern.[5]

Medication management strategies for patients treated with atypical antipsychotics should carefully weigh the risks and benefits of limiting access to therapy for this group in order to assure appropriate access. These patients, by nature of their disease, may be more susceptible to inadvertent consequences of formulary restrictions,[6] particularly with respect to medication adherence. While the health care industry has recognized poor adherence as a widespread problem for years, nonadherence can be particularly detrimental among patients with mental illnesses. Almost 80 percent of schizophrenic patients will have a relapse within one year after discontinuing antipsychotic treatment.[6] Medication nonadherence problems are common among patients with mental illness, resulting in more frequent acute psychotic episodes and hospitalizations,[7-9] in turn increasing cost burden for payors. Particular consideration should be given to the potential impact of restricting access to atypical antipsychotics — including the long-acting injectable products — for the severely mentally ill population, due to the risk of inadvertently exacerbating medication adherence problems, increasing medical spending, and ultimately failing to realize the expected cost-savings.

The Impact of Restrictive Formularies

Several studies have been conducted over the past 20 years to evaluate the impact of restricted access to antipsychotic medications, particularly atypical antipsychotics.[10-19] These studies analyzed the impact of formulary strategies on a range of factors, including the use of mental health services, number of hospitalizations, patient adherence, costs, and administrative burden. These studies yielded mixed results. While some studies reported evidence of successful use of formulary strategies to require clinical justification for use of some medications, others found that formulary management did not produce a clear benefit in terms of improving patient outcomes and lowering costs. The mixed outcomes highlight the importance of a thorough evaluation of risks and benefits, as well as the thoughtful implementation of formulary management strategies in order to minimize the risk of negative results and adverse health outcomes for this patient population.

Lu et al conducted a study of the unintended impact of a Medicaid prior authorization policy on access to medications for treatment of patients with bipolar disorder.[11] This study concluded that the implementation of the policy was associated with a decrease in the rate of initiation of treatment.[11] While this study was conducted before the availability of multiple generic atypical antipsychotic agents, the trend observed in this study was attributed to a decrease in the use of atypical antipsychotics, without a corresponding increase in initiation of therapy with formulary-preferred agents.[11] This same study did not identify any impact on members switching therapy among those who were currently taking a nonpreferred agent because they were permitted to continue treatment.[11] This may be viewed as

Controlling pharmaceutical costs is one of the many challenges faced by payors. Complicated disease states such as mental illnesses intensify this challenge. The impact of formulary restrictions on atypical antipsychotics yields mixed results in cost and patient outcomes.

demonstrating a best practice, ensuring that members who are currently stable should be allowed to continue their atypical antipsychotic therapy despite a change in formulary status. A cost analysis found that this policy change produced modest savings, which were attributed primarily to the increase in treatment discontinuation.[11] Ultimately, the state suspended the policy due to case reports of adverse health effects associated with the implementation of the restrictive formulary policy. The study authors concluded further research was required to evaluate the unintended consequences of prior authorization policies.

An analytic model was created in a study conducted by Abouzaid et al to compare the cost of schizophrenia treatment from a Medicaid perspective.[12] The model evaluated costs associated with a prior authorization policy in place versus no prior authorization. The analysis suggested adding a prior authorization policy yields a modest cost-savings about half of the time, and that slight increases in hospitalizations occurred, which can also make a prior authorization process more costly compared to open access.

In a survey of a sample of psychiatrists from the American Medical Association's Masterfile, a medication access problem was reported for nearly half of all patients.[13] The most common access problems included not being able to prescribe refills or new prescriptions, prescribing a medication not clinically preferred because a medication was not covered, and discontinuing medications as a result of prescription drug coverage or management issues.[13] Patients with medication access problems were three times more likely to experience adverse events compared with those without medication access problems. The study also found that states with more access issues had significantly higher adverse event rates.

The effect of removing a Medicaid restricted access policy against atypical antipsychotics has also been studied.[14] Open access to medications resulted in two atypical antipsychotic brands becoming the most expensive drugs for the state. However, the increased costs were found to be offset by lower overall expenditures per month per patient due to reductions in nursing home care and psychiatric hospitalizations. The results highlight the importance of giving consideration to the overall costs of care, rather than assessing pharmacy costs alone.

Increasing Copayments in a Commercial Population

The majority of published literature has assessed the impact of restricted access to atypical antipsychotic drugs based on the analysis of Medicaid claims data. To investigate the impact of atypical antipsychotic formulary controls in the commercial sector, an internal analysis was conducted using pharmacy claims data from a regional health plan.[20] The particular plan was selected based on a decision to change their formulary during the second quarter of 2012, which was soon after olanzapine, quetiapine, and ziprasidone became available as generics. The plan moved all of the branded atypical antipsychotics to a higher or nonpreferred tier, increasing copayments for patients on these therapies. Prior to the formulary change, three branded atypical antipsychotics were available on the preferred tier. The average branded atypical antipsychotic copayment of around $30 for a 30-day supply, prior to the formulary change, was increased to $50 per month one year after the policy changed.[20]

The analysis measured patients' adherence to their atypical antipsychotic for 12 months prior to the formulary change, compared with the 12 months following the change. The analyzed sample included members receiving only one atypical antipsychotic and who remained on the same medication during both study periods. The patients were divided into two groups: those who were treated with a product that moved to the higher tier (i.e., affected brand), and those who were either on a generic product or a product that became available as a generic during the study period (i.e., unaffected brand). The proportion of days covered (PDC) was used to assess adherence.[21]

Implementation of the policy change coincided with an increase in nonadherence. The analysis found that the members who were on an affected brand experienced a 7.4 percent decrease in PDC (81.9 percent in year one, compared with 74.5 percent in year two).[20] Although adherence can be expected to decrease over the duration of therapy, patients taking unaffected brand medications experienced a 2.1 percent decrease in PDC (85.0 percent in year one, 82.9 percent in year two).[20]

The proportion of patients whose adherence decreased after the formulary change was greater among the affected brands group. Of patients taking an affected brand, 58.4 percent experienced a decrease in adherence following the formulary change, compared with 47.7 percent of those who were not affected ($p < 0.01$).[20]

Using a PDC greater than or equal to 80 percent to define adherence, there was a 9.5 percent decrease in adherence among patients taking an affected brand ($p < 0.01$; 63.8 percent prior to the policy change, 54.3 percent following the change).[20] This finding is relevant when compared with a 2.3 percent decrease in adherence among patients whose treatments were not affected.[20] In a subgroup

analysis of patients adhering to medications prior to the policy change, a significantly higher proportion of nonadherence was observed in patients on an affected brand than in patients on an unaffected brand (31.8 percent vs. 19.8 percent; $p < 0.01$).[20]

From a formulary management perspective, one of the primary purposes of moving a branded product to a higher copayment tier is to incentivize providers and patients to use the lower-cost or preferred products. To help understand the effect the policy change may have had on the market share and total atypical antipsychotic spend, an analysis of the total health plan population was performed. The quarter prior to the formulary change was used as a baseline for analysis purposes, and the market share and spend during the same quarter in the subsequent year was used as a comparator. The combined market share of the three affected branded atypical antipsychotics demonstrated a slight decrease of 2.4 percent from Q1 2012 to Q1 2013. Interestingly, the combined olanzapine, quetiapine, and ziprasidone market share showed a corresponding increase of 2.4 percent over the same period.[20] Since all three of these atypical antipsychotics had recently become generically available prior to the formulary change, it is possible that their availability alone may have enticed some providers to utilize these treatments for their patients.

There was a 22.0 percent decrease, which equates to $1.82 million, in total atypical antipsychotic spend from Q1 2012 to Q1 2013.[20] This translates to an annualized savings of $7.2 million. However, total spend on quetiapine and ziprasidone alone decreased by $2.31 million during the same time period ($9.2 million annualized).[20] This suggests that the reason for the cost-savings may largely be due to the two commonly utilized products having gone off patent. It is also worth considering the impact of rebates on this analysis. Total spend may be overestimated, as it does not account for any rebates that the health plan may have been receiving from branded manufacturers. Likewise, cost-savings demonstrated after the formulary change may be overestimated since any rebate the health plan was receiving was likely decreased or eliminated once the originally preferred brands were moved to the nonpreferred tier.

This analysis had several limitations. The indication for treatment was not available through the pharmacy claims data, therefore there was no control for different diagnoses (bipolar disorder, schizophrenia, depression, etc.). Since the adherence analysis only studied patients who were on therapy prior to the policy change, it is not known what, if any, effect the policy had on patients who initiated therapy after the policy took place. Additionally, the analysis was conducted with data from this plan serving as its own control. The adherence from the cohort used in the study likely overstates the overall health plan adherence, since patients who discontinued treatment prior to the policy change or who did not have multiple fills in each study year were not included in the analysis. Administrative costs incurred by the health plan in implementing the formulary changes were not factored into the cost calculations.

The commercial analysis demonstrated that an increase in members' copayments for their atypical antipsychotic may lead to a decrease in adherence. Since medical data was not available for the analysis, it is not known if the decrease in adherence led to an increase in the use of mental health services, the major driver of total costs in this population. There was a decrease in pharmacy spend after the formulary change took place, but this trend was likely due to the increased generic availability of popular atypical antipsychotics. The decrease in pharmacy spend may have been accompanied by a partial offset as a result of a decrease in manufacturer rebates from the affected brands, although this was not calculated. Similar to the conclusions drawn from the majority of the Medicaid studies, it is difficult to assess if the formulary change succeeded in achieving the intended objective in this commercial scenario.

Challenges of Restricting Access in the Mental Illness Population

Formulary restrictions such as prior authorization policies require thoughtful consideration. Attention should be given to avoiding the creation of an unintended barrier to the treatment of bipolar and schizophrenic patients. Prior authorizations may increase administrative costs for the health plan, and may impact appropriate treatment and utilization by creating additional barriers for prescribers, with the possibility that restrictions or step therapy policies may lead to a decrease in prescribing. Adherence challenges might also occur for patients as they may be unaware that their medication requires a prior approval until after they reach the pharmacy. In these situations, the requirements of either completing the administrative approval process or switching medications may deter some patients from filling their prescriptions. Adding further complexity, as noted by Perry et al, is the reality that patients with chronic mental illnesses are more likely to be confused by administrative barriers, and may not understand the prior authorization process.[22] This scenario could result in some patients abandoning treatment to avoid the prior authorization process, and becoming immediately nonadherent.

Another potential consideration is that the response to antipsychotic medications, according to Case et al, is more likely to be individualized compared with that demonstrated with other chronic disease medications.[23] Studies indicate responses to specific atypical antipsychotics and the associated risks of adverse events vary widely.[24] Thus, if certain patients are more sensitive to adverse effects associated with formulary-preferred agents, a prior authorization policy could increase the incidence of unfavorable outcomes and contribute to medication discontinuation. Additionally, Koyanagi et al report physicians may be likely to prescribe a medication that may not be the ideal choice for a patient simply because requesting a prior authorization for a more appropriate medication is too time-consuming.[25]

Higher patient copayments can become a negative incentive for any chronic disease patient. Patients with mental illness in particular may not understand why their copayment has changed. Since these patients are so vulnerable, any disruption or additional challenge to their health care routine may increase the likelihood of treatment discontinuation or gaps in therapy.

Conclusion

Controlling pharmaceutical costs is one of the many challenges faced by payors. Complicated disease states such as mental illnesses intensify this challenge. The impact of formulary restrictions on atypical antipsychotics yields mixed results in cost and patient outcomes. It is important for payors and pharmacy benefit managers, in a collaborative manner, to thoroughly examine the implications across the entire scope of care when considering formulary restrictions on atypical antipsychotics, in an effort to avoid unintentional disruption of treatment or limiting access to optimal therapy for a particular patient. Due to large differences in clinical response and side effects among patients, the ability to select clinically appropriate atypical antipsychotics without formulary restrictions may enhance treatment outcomes.

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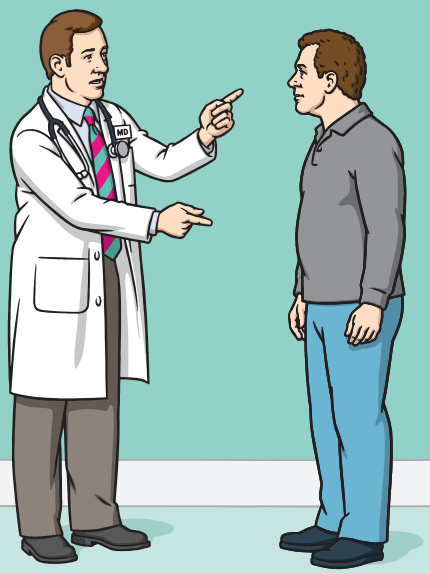
IN ADULT PATIENTS WITH CHRONIC NON-CANCER PAIN

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.

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Reference: 1. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), US Department of Health and Human Services. Abuse-Deterrent Opioids — Evaluation and Labeling: Guidance for Industry. April 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. Accessed August 25, 2015.