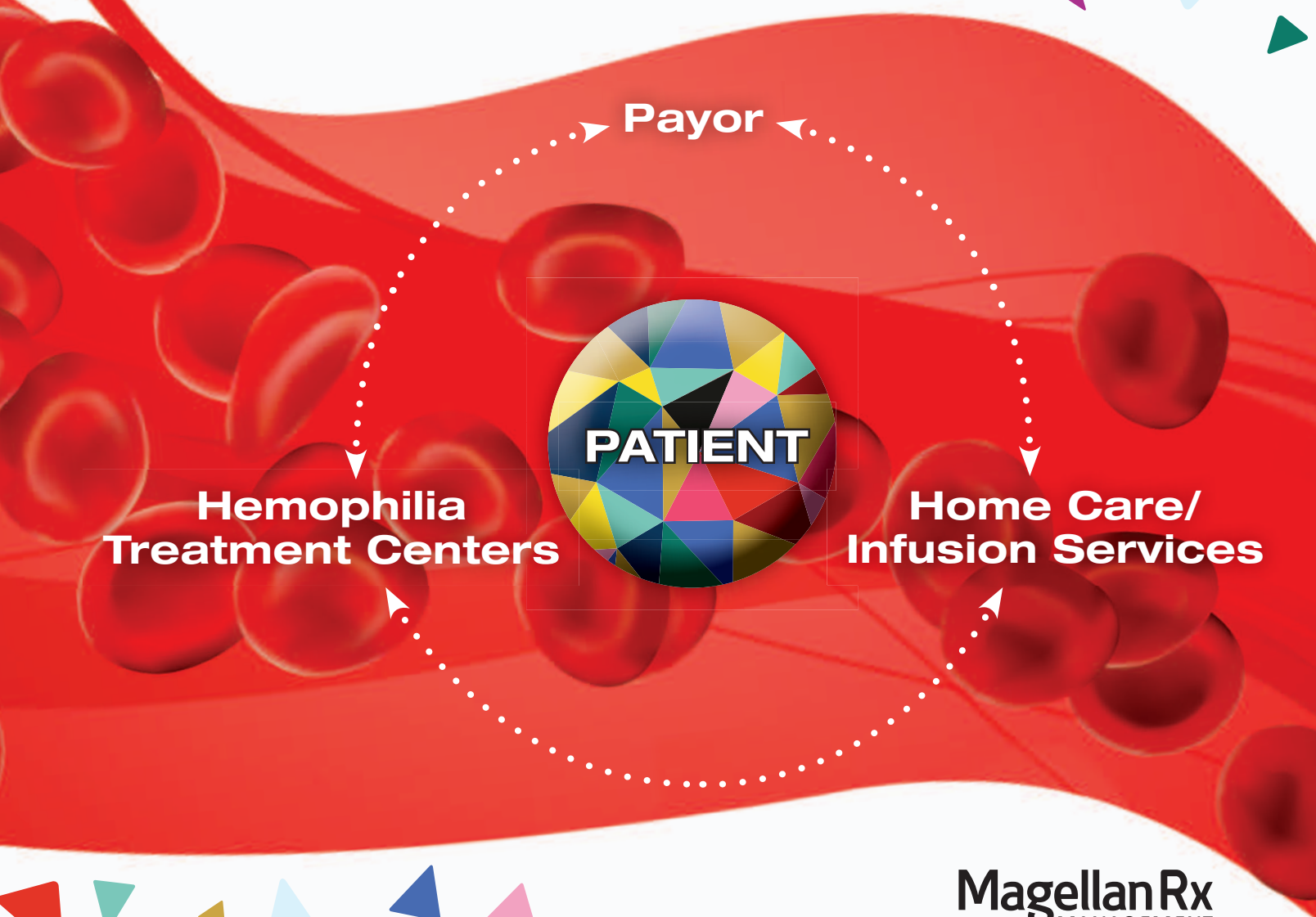
Summer 2015

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Hemophilia: Integrating Care to Improve Outcomes



Magellan Rx MANAGEMENT℠

www.magellanhealth.com

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.

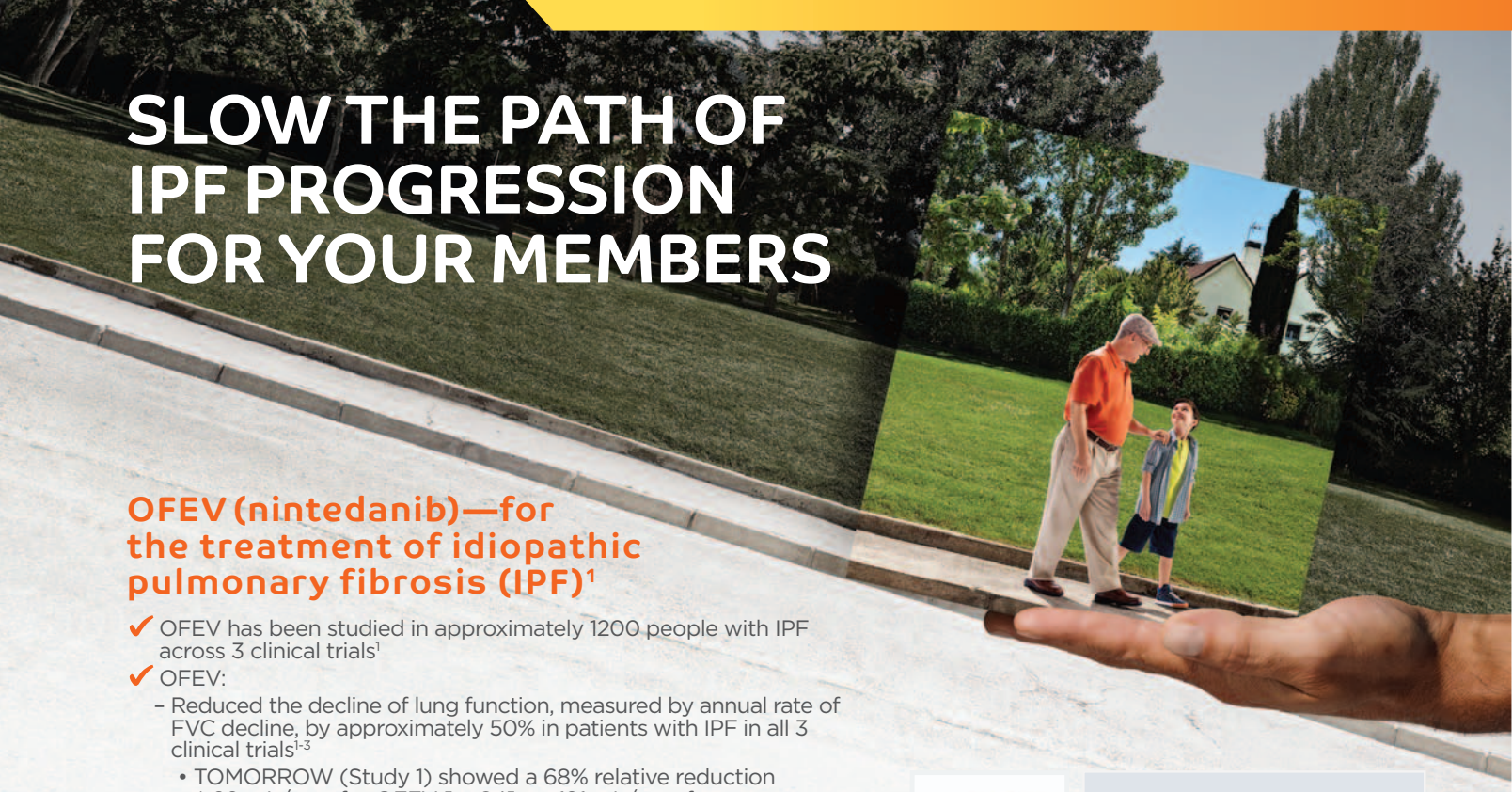
More detailed information is available upon request.

For information about Victoza® contact:
Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1–877-484-2869
Date of Issue: March 9, 2015
Version: 8
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

SLOW THE PATH OF IPF PROGRESSION FOR YOUR MEMBERS



OFEV (nintedanib)—for the treatment of idiopathic pulmonary fibrosis (IPF)[1]

- ✔ OFEV has been studied in approximately 1200 people with IPF across 3 clinical trials[1]
- ✔ OFEV:
  - Reduced the decline of lung function, measured by annual rate of FVC decline, by approximately 50% in patients with IPF in all 3 clinical trials[1-3]
    - TOMORROW (Study 1) showed a 68% relative reduction (-60 mL/year for OFEV [n=84] vs -191 mL/year for placebo [n=83]), difference=131, 95% CI=27, 235)[1,2]
    - INPULSIS®-1 (Study 2) showed a 52% relative reduction (-115 mL/year for OFEV [n=309] vs -240 mL/year for placebo [n=204]), difference=125, 95% CI=78, 173)[1,3]
    - INPULSIS®-2 (Study 3) showed a 45% relative reduction (-114 mL/year for OFEV [n=329] vs -207 mL/year for placebo [n=219]), difference=94, 95% CI=45, 143)[1,3]
  - Significantly reduced the risk of time to first acute IPF exacerbation over 52 weeks compared with placebo in 2 out of 3 clinical trials[1]
    - TOMORROW (investigator-reported): HR=0.16 (95% CI=0.04, 0.71)
    - INPULSIS®-1 (adjudicated): HR=0.55 (95% CI=0.20, 1.54; not statistically significant)
    - INPULSIS®-2 (adjudicated): HR=0.20 (95% CI=0.07, 0.56)

Not shown at actual size.

ONE CAPSULE, TWICE DAILY WITH FOOD[1]

THE TOTALITY OF THE EVIDENCE DEMONSTRATES THAT OFEV SLOWS DISEASE PROGRESSION[1,4-7]

To learn more about OFEV, please visit OFEV.com/formularykit

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.

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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Gastrointestinal Disorders (cont'd)

Nausea and Vomiting (cont'd)

- 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. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. **2.** Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087. **3.** Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;360(22):2071-2082. **4.** Zappala CJ et al. *Eur Respir J*. 2010;35(4):830-836. **5.** Schmidt SL et al. *Chest*. 2014;145(3):579-585. **6.** du Bois RM et al. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. **7.** Song JW et al. *Eur Respir J*. 2011;37(2):356-363.

Please see accompanying Brief Summary for OFEV on the following pages.

OFEV®
(nintedanib)
capsules 150mg

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]*.

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℞ only

Boehringer Ingelheim

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Letter from Magellan Rx

Dear Managed Care Colleagues,

Susan Petrovas, RPh

The wait is over for biosimilar products in the United States. The first biosimilar product has been approved, the FDA has released guidance documents regarding the approval pathway and manufacturer requirements, and several biosimilar products are currently under review and likely to be approved within the next six to 12 months. The first biosimilar approval — Zarxio™ (filgrastim-sndz) — has helped address many questions relating to the biosimilar approval process, provision of indications, and even CMS reimbursement, but will the savings generated from biosimilars be what we have anticipated? The answer to this question is dependent on a variety of product-specific factors and marketplace dynamics that remain unknown at this time.

Obviously, the cost difference between biosimilars and reference products remains a major question. However, an equally important consideration is the ability of these biosimilar products to obtain an optimal market share to achieve the desired savings. Since biosimilars require limited clinical trial evidence to support their approval, physicians may not be comfortable utilizing these products, especially for sensitive or complicated patients. The impact this will have on the uptake of biosimilars and their ability to obtain market share is unknown and will likely be category- or even product-specific.

So how can we optimize the cost-savings potential of biosimilars? It appears evident that each biosimilar product/category must be evaluated independently. Unique management strategies for each biosimilar approval should be explored to ensure appropriate clinical management and optimization of cost-savings. For each product/category, payors will have to evaluate the clinical and financial implications of the biosimilar entrant and decide whether to continue supporting the reference product or pursue opportunities with competitive biosimilars. This decision will depend on the product characteristics, patient and physician dynamics, benefit (medical vs. pharmacy), and ability to achieve a desired market share, among other factors. Additionally, accurate forecasting will be instrumental in organizational decision making regarding the economic benefit of biosimilar products.

Stay tuned for upcoming issues of *Magellan Rx Report* in which we will be reviewing the biosimilar landscape in detail, providing real-world assessments of new-to-market biosimilar products, and evaluating the cost-effectiveness of these therapies. Magellan Rx Management is committed to providing our payor clients with innovative approaches to addressing the escalating specialty spend, including customized strategies for biosimilar management. We offer integrated solutions that combine our medical, specialty, and pharmacy benefit expertise, allowing us to leverage our collective scale and experience in managing total drug spend for our payor 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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MANAGED CARE NEWSSTAND

New Model of Care Improves Rheumatoid Arthritis Outcomes, Reduces Costs

A new rheumatoid arthritis (RA) care model produced significant quality of care improvements and reduced costs in more than 2,300 patients over a 22-month period. By reducing use of costly biologics, researchers reported a cost-savings of $720,000 during the first year. The projected cost-savings for the second year was $1.2 million.

Forty percent of participants met all applicable quality measures at the end of the study compared with only 22 percent when the study started. In addition, the percentage of patients in remission or with low disease activity rose from 35 to 53 percent.

The care model — called Attribution, Integration, Measurement, Finances, and Reporting of Therapies, or AIM FARTHER — features several components including: registry development, integration of primary and specialty care, a new approach to care, defining roles and attribution, task management and performance reporting, and a new financial incentive model.

Source: Geisinger-developed rheumatoid arthritis care model improves care, reduces cost: Results presented at recent American College of Rheumatology annual scientific meeting. Geisinger Health System. News release. December 8, 2014.

Patient Outcomes Improve with PCSK9 Inhibitors

A study of nearly 4,500 patients found that those treated with evolocumab — a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitor) — for one year achieved better clinical outcomes than participants who received standard care for high cholesterol. Study participants taking PCSK9 inhibitors demonstrated a 53 percent reduction in cardiovascular events, including death, heart attack or stroke, hospitalizations or angioplasty, when compared with patients receiving standard care. Most individuals in the standard care group were on moderate or high levels of statin medications.

Researchers reported that the rate of cardiovascular events in the group receiving standard care for one year was 2.18 percent. The rate in the PCSK9 group was about half, at 0.95 percent for the same time period.

The average low-density lipoprotein (LDL) cholesterol level of participants at the start of the study was 120 milligrams per deciliter. The LDL levels of those who received evolocumab dropped an average of more than 70 milligrams per deciliter during the study.

"The reduction in LDL was profound and that may be why we saw a marked reduction in cardiovascular events so quickly," said lead author Marc Sabatine, MD, of Brigham and Women's Hospital.

Source: After one year, patients on new drug fare better than standard therapy: Study provides cardiovascular outcomes results from new class of cholesterol-lowering medications. American College of Cardiology. News release. March 15, 2015.

CMS Launches 'Next Generation' Accountable Care Organization Model

The Centers for Medicare & Medicaid Services' Innovation Center has created a new model of payment and health care delivery, the Next Generation Accountable Care Organization (ACO). Developed under the Affordable Care Act, the Next Generation ACO is intended to focus on attaining high-quality standards of care and establishing predictable financial targets. It also gives providers and beneficiaries additional opportunities to work together to coordinate care.

The new model ACOs will include additional performance risk and potential for sharing a higher portion of savings than the current ACO model. To offset the risk, the new ACOs will have more stable benchmarks and flexible payment options to assist with funding care improvement efforts.

"The Next Generation ACO Model is one of many innovative payment and care delivery models created under the Affordable Care Act, and is an important step toward advancing models of care that reward value over volume in care delivery," said U.S. Department of Health & Human Services Secretary Sylvia M. Burwell. "This model is part of our larger effort to set clear, measurable goals and a timeline to move the Medicare program — and the health care system at large — toward paying providers based on the quality, rather than the quantity of care they give patients."

Source: Affordable Care Act initiative builds on success of ACOs. U.S. Department of Health & Human Services. News release. March 10, 2015.

More-Informed Women Make Better Breast Screening Decisions

Women who understand more about mammography screening and the risk of overdetection and overdiagnosis report they are less likely to have the breast screening test, a new study reports. This is the first study to analyze the effect of including overdetection information in the decision support materials for women ages 48 to 50 who are about to be candidates for mammography screenings.

The study included nearly 900 women. The researchers compared the attitudes of women who received decision support materials that included information about overdetection versus a control group that received the same materials with all content pertaining to overdetection omitted. The decision support materials contained evidence-based details about breast cancer screening outcomes over a 20-year period.

Researchers found that women who received the additional information:

- Were more likely to have the knowledge they needed to make informed decisions
- Viewed mammography screening less favorably, however, overall attitudes remained positive
- Were less likely to say they planned to have mammograms

The researchers say there is a shift away from uninformed approaches to screening to providing balanced information to help women make their own informed choices about breast cancer screening.

Source: Breast cancer: Women told of over-diagnosis make better screening choices. The University of Sydney. News release. February 18, 2015.

Study Highlights Need for Improved Care for Hepatitis C

A study of the hepatitis C (HCV) patient care continuum in a U.S. urban area found that many infected patients are falling through the cracks at different stages of the treatment process, which includes: screening, disease confirmation, care, and treatment.

Researchers used the U.S. Census Bureau and other national data which estimated that 2.9 percent of Philadelphia residents were infected with HCV. During the study period, nearly 13,600 HCV-positive results were sent to the Philadelphia Department of Public Health. Of those who tested positive, only 27 percent were in care and only 15 percent had been treated or were receiving treatment for HCV.

"The fact that so few patients with HCV are making it to treatment underscores the need to build awareness of the importance of screening and continued care among at-risk groups," said Kendra Viner, PhD, MPH, from the public health department.

The researchers say understanding why patients are not receiving treatment is key to improving care for those with HCV.

Source: Preventing hepatitis C patients from being lost in the health care system. *Hepatology.* News release. December 18, 2014.

Immediate Treatment Effective for Hereditary Angioedema

Italian researchers found that on-demand treatment is effective in reducing disease-related morbidity in patients with hereditary angioedema with C1 Inhibitor Deficiency (C1-INH-HAE). They studied 227 patients with C1-INH-HAE from January 2009 to August 2014. The participants wrote in diaries about their attacks, including: the location, the severity, medications used to treat them, the duration of treatment, and more.

During the study period, participants reported 4,244 attacks. The median duration of 2,393 attacks was 10 hours with approved therapies. The mean duration of attacks when no treatment was used was 45 hours. Attacks treated with tranexamic acid had a median duration of 38 hours.

The researchers noted that more patient education is needed because this approach is used in only 50 percent of attacks.

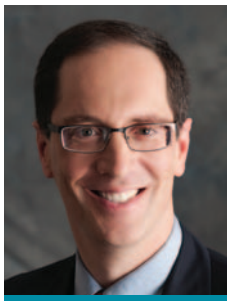
Source: Mansi M, et al. On demand therapy in hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE): Prospective observational study of 4,244 attacks. American Academy of Allergy, Asthma and Immunology Annual Meeting. Houston, February 20-24, 2015. Abstract.

Specialty Patient-Centered Medical Home: Moving Beyond Primary Care

Chronis Manolis, RPh, VP Pharmacy and Chief Pharmacy Officer, UPMC Health Plan

Miguel Regueiro, MD, Professor of Medicine; Professor, Clinical and Translational Science, University of Pittsburgh School of Medicine; Associate Chief, Education Clinical Head, and Co-Director, Inflammatory Bowel Disease Center

Chronis Manolis, RPh



Miguel Regueiro, MD

Federal regulators, medical associations, and employer groups have embraced the patient-centered medical home (PCMH) as a model to transform the American health care system by improving quality, lowering costs, and increasing patient and provider satisfaction.[1,2] The comprehensive care that PCMHs offer is increasingly playing a role in Accountable Care Organizations (ACOs) as health care shifts away from the traditional fee-for-service model to a team-based care approach that rewards performance. While the exact number of PCMHs is difficult to quantify, adoption of the model's focus on comprehensive and coordinated care that reduces waste is increasingly drawing interest as a framework for specialty care.[3,4] The manner by which specialty services integrate into the PCMH model varies according to the nature of the specialty care required. For example, dermatologists most often offer consultative support. Cardiologists or gastroenterologists are likely to focus on evaluation and treatment, while oncologists or nephrologists are poised to play an active role that may include the permanent or temporary assumption of care or co-management of patients with primary care physicians.[4]

The desire for greater efficiency and effectiveness in treating patients with chronic conditions is inherent in PCMHs and specialty medical homes, and is being driven by the Affordable Care Act. High-risk and high-utilization patients account for a disproportionate portion of health care expenditures. While almost half of the population makes infrequent visits to health care providers, 5 percent of the population accounts for nearly half of all health care costs.[5] The needs of this subset of high health care utilizers are driving the appeal and adoption of the PCMH model.

An Evolving Model

The medical home approach was created in 1967 as a way to better treat children with special health needs.[6] PCMHs continue to evolve today as some physicians who treat chronic illnesses such as congestive heart failure, diabetes, and asthma find they also serve as some patients' specialists.[7] While specialists such as cardiologists, endocrinologists, and pulmonologists may serve as the primary care provider for only a small proportion of their patients,[8] the American College of Physicians

(ACP) has adopted the position that specialty practices providing principle care for chronic conditions should be considered medical homes.[9]

The National Committee for Quality Assurance (NCQA), the quality oversight organization that sets standards for PCMHs, also recently extended medical-home concepts to specialists by establishing patient-centered specialty practice (PCSP) standards. Specialty practices that seek NCQA recognition commit to standards related to care coordination, access to specialty care, reduction of duplicative or unnecessary tests, improved communication, and performance measurement/improvement.[10] The criteria are included in Figure 1.[11] Nearly 700 specialty practices have earned NCQA recognition to date.[12] The PCSPs include those providing treatment for autism, vascular disease, infectious disease, occupational health, cancer, diabetes, orthopedics, women's health, and rheumatoid arthritis. Based on the medical neighborhood model developed by the ACP and the Agency for Healthcare Research and Quality (AHRQ), specialty medical homes have the opportunity to provide greater value through the PCMH model.[13,14]

Specialty Medical Homes

One example of an initiative to establish a specialized medical home with the objective of tailoring the PCMH to patients who require frequent care by specialists is underway at the University of Pittsburgh Medical Center (UPMC). In collaboration with UPMC Health Plan, UPMC established a medical home for patients with inflammatory bowel disease (IBD). UPMC already operated an IBD Center; the site had experienced a 30 percent increase in new patients and an 18 percent increase in total number of patients over a three-year period. Data demonstrated that 15 percent of UPMC's IBD patients accounted for 48 percent of total expenditures. Of these costs, pharmacy, injectable drugs, and surgery represented the top three expenditures for IBD patients.

Believing that an opportunity for improvement existed, UPMC and the UPMC Health Plan began considering how to establish an IBD medical home that would provide high-quality, comprehensive, cost-effective, patient-centered health care for patients with Crohn's disease and ulcerative colitis. UPMC launched the IBD medical home among 722 of the health plan's high-utilization patients. Building on the suggestion that high-utilization patients with chronic conditions often experience concomitant mental illness, pain, and poor social support,[15] UPMC developed a three-pronged approach to address these needs by providing resources around behavioral skills, social support, and stress reduction training. The BEST CARE approach is designed to help the more than 50 percent of UPMC's IBD patients who have pain, stress, coping difficulties, anxiety/depression, and fatigue that lead to worsening of their disease and increased health care utilization. Psychiatrists, psychologists, and social workers are available around the clock and participate in the co-development of

Elements of the PCMH

Although definitions of the patient-centered medical home (PCMH) vary,[1] the Agency for Healthcare Research and Quality has identified the following five attributes of the PCMH care model[2]:

Comprehensive care — Teams of multidisciplinary providers are responsible for meeting a patient's health needs. This includes prevention and wellness activities, as well as treatment for acute, chronic, and mental health conditions.

Patient-centered care — Providers engage and educate each patient in order to establish collaborative care plans that respect individual needs, preferences, values, and goals.

Coordinated care — Providers coordinate care for a patient with other members of the care team, the patient and the patient's family, and delivery settings. Care sites may include hospitals, home health care, or specialty facilities, as well as community services.

Access to care/services — Expanded hours, shorter wait times, and continuous telephone and electronic access to caregivers make it easier for a patient to receive needed services.

Safe, quality care — A systems-based approach to safe, quality care includes use of evidence-based medicine and clinical decision-support guidelines. Performance measurement, sharing and acting upon safety data, and use of information about patient experience/satisfaction are also used in efforts to improve care.[3,4]

REFERENCES
1. Expanding the toolbox: Methods to study and refine patient-centered medical home models. Agency for Healthcare Research and Quality website. **http://pcmh.ahrq.gov/sites/default/files/attachments/ExpandingtheToolkit_031513comp.pdf.** Accessed March 30, 2015.
2. Crabtree BF, Nutting PA, Miller WL, et al. Summary of the national demonstration project and recommendations for the patient-centered medical home. *Ann Fam Med*. 2010;8(suppl 1):S80-S90.
3. Jackson GL, Powers BJ, Chatterjee R, et al. The patient-centered medical home: A systematic review. *Ann Intern Med*. 2013;158(3):169-178.
4. Defining the PCMH. Agency for Healthcare Research and Quality website. **http://pcmh.ahrq.gov/page/defining-pcmh.** Accessed March 30, 2015.

Figure 1: PCMH 2014 (6 standards/27 elements/100 points)[11]

1) Patient-Centered Access (10)
- A. Patient-Centered Appointment Access*
- B. 24/7 Access to Clinical Advice
- C. Electronic Access

2) Team-Based Care (12)
- A. Continuity
- B. Medical Home Responsibilities
- C. Culturally and Linguistically Appropriate Services
- D. The Practice Team*

3) Population Health Management (20)
- A. Patient Information
- B. Clinical Data
- C. Comprehensive Health Assessment
- D. Use Data for Population Management*
- E. Implement Evidence-Based Decision Support

4) Care Management and Support (20)
- A. Identify Patients for Care Management
- B. Care Planning and Self-Care Support*
- C. Medication Management
- D. Use Electronic Prescribing
- E. Support Self-Care & Shared Decision-Making

5) Care Coordination and Care Transitions (18)
- A. Test Tracking and Follow-Up
- B. Referral Tracking and Follow-Up*
- C. Coordinate Care Transitions

6) Performance Measurement and Quality Improvement (20)
- A. Measure Clinical Quality Performance
- B. Measure Resource Use and Care Coordination
- C. Measure Patient/Family Experience
- D. Implement Continuous Quality Improvement*
- E. Demonstrate Continuous Quality Improvement
- F. Report Performance
- G. Use Certified EHR Technology

**Must-pass*

treatment plans for patients with IBD to help patients reduce stress and improve coping abilities. While the BEST CARE approach is in the early stages of implementation, preliminary results indicate the metrics for primary care physician visits, IBD clinic visits, emergency department (ED) visits, and hospital admissions are improving.

The UPMC TOTAL CARE IBD medical home also seeks to optimize surgery for Crohn's disease and ulcerative colitis patients by considering medication alternatives. All patients are discussed by gastroenterologists and surgeons to determine collectively the appropriateness of surgery. The PCMH's gastroenterologists and surgeons also hold twice-weekly IBD management meetings and rely on clinical care pathways to optimize the timing or need for surgery. Other pharmacy and drug-utilization strategies include implementing evidence-based care pathways for appropriate use of biologics or lower-cost biosimilars. UPMC's TOTAL CARE IBD medical home also seeks to improve patient outcomes and reduce costs through use of:

- Physician Quality Reporting System (PQRS) measures for IBD[16]
- Preventive health activities such as vaccinations, bone health screenings, and smoking-cessation counseling
- Clinical pathways included in the electronic medical record (EMR)
- Telemedicine and virtual technology
- Patient satisfaction surveys
- Voluntary peer-to-peer connections for IBD patients

UPMC is now collecting and analyzing data from the IBD medical home pilot, with the potential aim of employing the medical home framework for treating other chronic diseases such as rheumatoid arthritis and multiple sclerosis.

Another initiative, the Michigan Oncology Medical Home Demonstration Project (MOMHDP), includes four oncology practices and 29 physicians. The oncology home is sponsored by Priority Health, Physician Resource Management, and ION Solutions. Components of the oncology medical home, which focuses upon Priority Health patients receiving chemotherapy, include:

- Use of evidence-based treatment guidelines and compliance tracking
- Automated physician order entry
- A patient portal
- Symptom management/standardized nurse triage
- Advanced care planning

The initial phase of the project sought to use this coordinated approach to deliver evidence-based treatments that would improve the management of chemotherapy side effects and

reduce costs through fewer patient hospitalizations and ED visits. The next phase of the project will introduce a survivorship program, patient distress screening, imaging guidelines, and standardized patient satisfaction surveys.[17]

MOMHDP includes an innovatively structured financial design. Rather than calculating payments for prescription medications based on the average sales price payment model, MOMHDP offers providers a drug acquisition reimbursement and care management fee that is calculated to increase total drug reimbursement. Providers also receive reimbursement for chemotherapy and treatment planning, along with advanced care planning consultation. In addition, participating physicians are eligible for shared savings opportunities.

During its first year, MOMHDP reported significant decreases in ED visits and inpatient admissions as compared to a control group. Through the effective management of this typically high-cost patient population, the demonstration project showed an estimated savings of $550.33 per patient.[17]

Specialty ACOs

In addition to medical homes for patients who require care from specialists, disease-specific ACOs are being evaluated as a means of providing patient-centered quality care. ACOs are groups of doctors, hospitals, and other care providers who come together voluntarily to give coordinated care to their Medicare patients.[18] The Centers for Medicare & Medicaid Services (CMS) has unveiled end-stage renal disease (ESRD) and oncology care ACO models in an effort to provide better care for patients with kidney failure or cancer patients who require chemotherapy. Both of these patient populations present care-coordination and cost-containment challenges. Patients with ESRD often suffer from comorbidities and have high rates of hospitalization.[19] ESRD patients represent 1.3 percent of Medicare beneficiaries, yet account for an estimated 7.5 percent, or $20 billion, of Medicare spending.[19] Likewise, chemotherapy costs incurred on behalf of cancer patients can easily exceed $10,000 per month, representing a significant cost factor and management challenge, given that a majority of the more than 1.6 million people diagnosed annually with cancer are Medicare beneficiaries.[20]

CMS announced the ESRD initiative in 2013 and is still seeking to partner with groups of health care providers, such as dialysis facilities, nephrologists, and suppliers, in order to establish what it refers to as ESRD Seamless Care Organizations (ESCOs). CMS is attempting to ensure the patient's voice is heard in ESCOs by requiring that these organizations have at least one patient representative or an independent consumer advocate on their governing board. ESCOs will assume clinical and financial responsibility for all care — not just for dialysis care or for care specifically related to a patient's ESRD. ESCOs must agree to provide care for a minimum of 350 Medicare beneficiaries. Enrollees in the program should have previously received care from one of the ESCO participating providers. In addition to using a set of quality measures to assess ESCO performance, CMS plans to assess utilization of services by ESCO-enrolled beneficiaries and to conduct patient experience surveys annually. CMS had set a start date of July 1, 2015, for the ESRD initiative.[19]

Like the ESRD initiative, CMS's Oncology Care Model (OCM) is designed to align financial incentives to improve care coordination, appropriateness of care, and access to care. First announced in February 2015, OCM will offer participating practices episode-based payments for cancer patients treated with nontopical chemotherapy. As of May 2015, details of the OCM are still being released. Future updates will be available at the CMS Innovation Center.[21] Participating practices will receive $160 per beneficiary each month for Medicare beneficiaries receiving treatment with an included chemotherapeutic agent during each month of a session, regardless of cancer type.[22] The program will also include the potential for a performance-based payment for sessions of chemotherapy care; these incentives will only be available for beneficiaries with cancers deemed high-volume, and for which reliable benchmarks can be calculated. Although the list of high-volume cancers has not yet been released, CMS estimates that the high-volume cancers that can be benchmarked will cover 90 percent of Medicare beneficiaries receiving chemotherapy.[22] CMS has plans to initiate the OCM program in spring 2016.

Lessons Learned

Although there is a great deal of interest in new delivery and payment models, most providers are not in PCMHs, PCSPs, or even ACOs.[14] The shift to these new models of care will require many changes for providers. For example, provider practices that are not part of a PCMH, PCSP, or ACO often collaborate with a hospital or medical center. As a result, the practice is built around the health care team and its structure, rather than around the patient or the patient's illness. Specialty providers in this traditional model act as consultants and see patients who are referred by other providers. Payment is based on volume, and there is institutional support from downstream revenue (e.g., surgery, pathology, radiology, infusion).

In a PCMH, PCSP, or ACO, providers collaborate with private or public insurers in a model designed to be patient-centered. Specialists, to whom patients are referred by the payor, can act as principal care providers. Acting as the primary care provider is likely to require specialists to redesign their practices to provide the range of services required of a medical home.[7] Specialty practices also need adequate time to incorporate the clinical standardization that is the foundation of the medical home and ACO models.[17]

Payment methodology in the PCMH represents another significant change. Rather than being compensated based on volume or activity, providers are rewarded financially for creating value through coordinated care, access to care (e.g., telemedicine, point-of-contact mental health care), preventive medicine, and other strategies that lead to improved health outcomes and lower health costs. In the MOMHDP, collaboration between providers and payors was identified as a factor in improved clinical and financial outcomes. Transparent use and cost data were identified as fundamental to the partnership between payors and providers.[17]

The complexities of engaging in these new health care delivery models may require an uptake time frame of up to 10 years to support measuring and demonstrating health and economic impacts.[23] Relying on analyses of short-term cost savings or on data from fragmented performance measures currently in place may not accurately depict how practice and patient transformations combine with new reimbursement models to optimize care.[23] Data analysis to demonstrate the financial and clinical impact of PCMHs and PCSPs will be sought and valued as a means of demonstrating the ongoing value of these innovative care models.

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References

1. Expanding the toolbox: Methods to study and refine patient-centered medical home models. Agency for Healthcare Research and Quality website. **http://pcmh.ahrq.gov/sites/default/files/attachments/ExpandingtheToolkit_031513comp.pdf.** Accessed March 30, 2015.
2. Crabtree BF, Nutting PA, Miller WL, et al. Summary of the national demonstration project and recommendations for the patient-centered medical home. *Ann Fam Med*. 2010;8(suppl 1):S80-S90.
3. Klein DB, Laugesen MJ, Liu N. The patient-centered medical home: A future standard for American healthcare? *Pub Admin Rev*. 2013;73(s1):S82-S92.
4. Huang X, Rosenthal M. Transforming specialty practice—the patient-centered medical neighborhood. *N Engl J Med*. 2014;370:1376-1379.
5. Cohen S, Yu W. The concentration and persistence in the level of health expenditures over time: Estimates for the U.S. population, 2008–2009. Statistical Brief #354. Agency for Healthcare Research and Quality website. **www.meps.ahrq.gov/mepsweb/data_files/publications/st354/stat354.shtml.** January 2012. Accessed March 30, 2015.
6. What is a medical home? Why is it important? U.S. Department of Health and Human Services Health Information Technology website. **www.hrsa.gov/healthit/toolbox/Childrenstoolbox/BuildingMedicalHome/whyimportant.html.** Accessed March 30, 2015.
7. Casalino LP, Rittenhouse DR, Gillies RR, et al. Specialist physician practices as patient-centered medical homes. *N Engl J Med*. 2010;362(17):1555-1558.
8. Clarification document regarding the patient-centered medical home and specialty and subspecialty practices. Medscape website. **www.medscape.com/viewarticle/589666.** Accessed March 30, 2015.
9. Patient-centered specialty practice frequently asked questions. National Committee for Quality Assurance website. **www.ncqa.org/Programs/Recognition/Practices/PatientCenteredSpecialtyPracticePCSP/PatientCenteredSpecialtyPracticeFAQs.aspx.** Accessed March 30, 2015.
10. Recognition directory. National Committee for Quality Assurance website. **http://recognition.ncqa.org/PSearchResults.aspx?state=&rp=8.** Accessed March 30, 2015.
11. NCQA 2014 patient-centered medical home recognition: Behind the enhancements. National Committee for Quality Assurance website. **www.ncqa.org/Portals/0/Events/BehindtheEnhancements_FINAL.pdf.** Accessed March 30, 2015.
12. The patient-centered medical home neighbor: The interface of the patient-centered medical home with specialty/subspecialty practices. American College of Physicians website. **www.acponline.org/advocacy/current_policy_papers/assets/pcmh_neighbors.pdf.** Accessed March 30, 2015.
13. Taylor EF, Lake T, Nysenbaum J, et al. Coordinating care in the medical neighborhood: Critical components and available mechanisms. Agency for Healthcare Research and Quality website. **http://pcmh.ahrq.gov/sites/default/files/attachments/Coordinating%20Care%20in%20the%20Medical%20Neighborhood.pdf.** June 2011. Accessed March 30, 2015.
14. The future of patient-centered medical homes: Foundation for a better health care system. National Committee for Quality Assurance website. **www.ncqa.org/Portals/0/Public%20Policy/2014%20Comment%20Letters/The_Future_of_PCMH.pdf.** 2014. Accessed March 30, 2015.
15. Schwenk TL. The patient-centered medical home: One size does not fit all. *J Am Med Assoc*. 2014;311(8):802-803.
16. The physician quality reporting system. American Gastroenterological Association website. **http://168.143.180.154/practice/quality-initiatives/cms-physician-qualitative-report-initiative.** Accessed March 30, 2015.
17. Kuntz G, Tozer J, Snegosky J, et al. Michigan Oncology Medical Home Demonstration Project: First-year results. *J Oncol Pract*. 2014;10(2):104.
18. Accountable Care Organizations (ACO). Centers for Medicare & Medicaid Services website. **www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO/index.html.** Accessed March 30, 2015.
19. Comprehensive ESRD care initiative. Centers for Medicare & Medicaid Services website. **http://innovation.cms.gov/initiatives/comprehensive-esrd-care/.** Accessed March 30, 2015.
20. Oncology care model. Centers for Medicare & Medicaid Services website. **http://innovation.cms.gov/initiatives/Oncology-Care/.** Accessed March 30, 2015.
21. The CMS Innovation Center. Centers for Medicare & Medicaid Services website. **http://innovation.cms.gov/.** Accessed April 24, 2015.
22. Oncology care model frequently asked questions. Centers for Medicare & Medicaid Services website. **http://innovation.cms.gov/Files/x/ocmfaqs.pdf.** Accessed March 30, 2015.
23. Stange KC, Nutting PA, Miller WL, et al. Defining and measuring the patient-centered medical home. *J Gen Intern Med*. 2010;25(6):601-612.

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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.

Selected Important Safety Information

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

Please see Brief Summary of full Prescribing Information on the following pages.
This information is not intended to replace discussions with your healthcare provider.

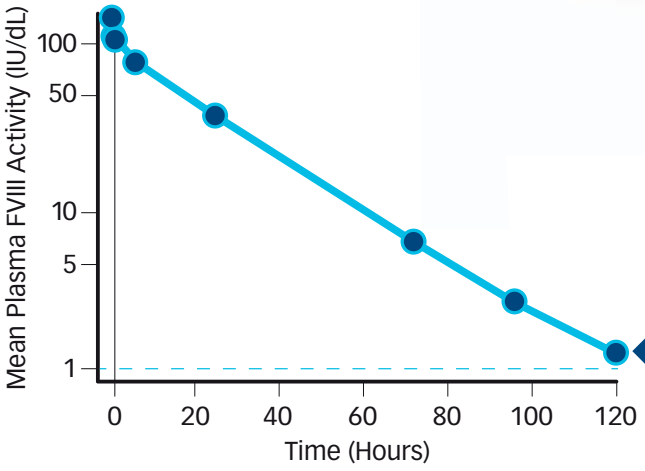
biogen idec®

ELOCTATE

THE FIRST AND ONLY rFVIII WITH A PROLONGED HALF-LIFE

5 DAYS WITH FACTOR LEVELS ABOVE 1%

MEAN FACTOR ACTIVITY PROFILE AFTER A SINGLE DOSE (50 IU/kg)*



ABOVE 1%

MEAN TERMINAL HALF-LIFE AFTER A SINGLE 50 IU/kg DOSE IN ADULTS*†

19.7 HOURS (17.4, 22.0)

Mean terminal half-life after a single 50 IU/kg dose in pediatric and adolescent patients*†‡

- 16.4 (14.1, 18.6) hours in subjects 12 to 17 (n=11)
- 14.6 (11.5, 17.7) hours in subjects 6 to 11 (n=27)
- 12.0 (9.55, 14.4) hours in subjects 2 to 5 (n=10)

*The pharmacokinetics of ELOCTATE were evaluated following a single dose of 50 IU/kg in the Phase 3 study of 28 adults and 11 adolescent, previously treated patients (ages 12 to 17 years), and in an open-label, multicenter study of 37 pediatric, previously treated patients (ages 2 to 5 years and 6 to 11 years).

†Presented in arithmetic mean (95% CI).

‡Compared to adults and adolescents, clearance was higher in children 2 to 5 years of age, indicating a need for dose adjustments. For patients 6 years and older, dose adjustment is not required.

Selected Important Safety Information

- Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Immediately discontinue ELOCTATE and initiate appropriate treatment if hypersensitivity reactions occur

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

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PROPHYLAXIS STARTING WITH
50 IU/kg EVERY 4 DAYS

- Regimen may be adjusted based on patient response in the range of 25 to 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
- After administering ELOCTATE, the one-stage clotting assay or chromogenic assay can be used to monitor plasma Factor VIII levels

WITH INDIVIDUALIZED PROPHYLAXIS
PROVEN PROTECTION[§] FROM BLEEDS

MEDIAN ANNUALIZED BLEED RATE[‖¶]

Overall Bleeds	1.60 (0.00, 4.69)	On-Demand	33.57 (21.14, 48.69)
Joint Bleeds	0.0 (0.00, 3.11)	On-Demand	22.76 (15.07, 39.02)
Spontaneous Bleeds	0.0 (0.00, 2.03)	On-Demand	20.24 (12.21, 36.81)

0 bleeds in **45%** of patients

[§]Protection is the prevention of bleeding episodes using a prophylaxis regimen.

[‖]Median (interquartile range 25th and 75th percentiles).

[¶]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 to 65 years) with severe Hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe Hemophilia A) that compared the efficacy of each of 2 prophylactic treatment regimens (individualized interval and fixed weekly) to episodic (on-demand) treatment. Hemostatic efficacy was determined in both: 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.

SAFETY FROM A-LONG CLINICAL TRIAL

Zero inhibitors, no anaphylaxis, and low incidence of adverse reactions (ARs)

- Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests
- One 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
- 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
- The most common ARs in the Phase 3 clinical study were arthralgia and malaise (each 1.2%) and: abdominal pain, lower; abdominal pain, upper; angiopathy[#]; bradycardia; chest pain; cough; dizziness; dysgeusia; feeling cold; feeling hot; headache; hypertension; joint swelling; myalgia; procedural hypotension; and rash (each 0.6%). 2 subjects were withdrawn from study due to ARs of rash and arthralgia

[#]Vascular pain after injection of study drug.

Find out more at ELOCTATEpro.com

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

This information is not intended to replace discussions with your healthcare provider.

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

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)

(continued)

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

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%)
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]

Hemophilia Management: Opportunities for Payor, Provider, and Home Care Coordination

James T. Kenney, Jr., RPh, MBA, Manager, Specialty and Pharmacy Contracts, Harvard Pilgrim Health Care

James T. Kenney, Jr., RPh, MBA

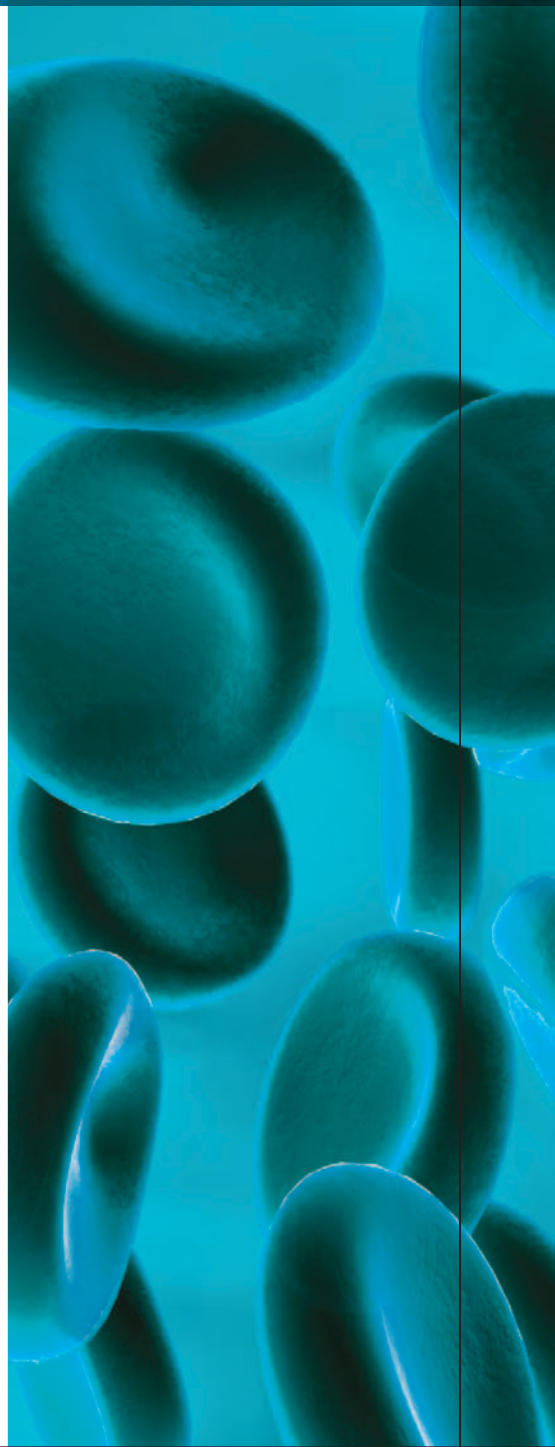
Comprehensive preventive care of hemophilia patients reduces morbidity and mortality, but there are inconsistencies in the strategies used by payors, providers, and home infusion organizations in managing this rare blood disorder.[1,2] Variations in the methods for the treatment and assessment of patient outcomes by stakeholders results in a variety of different programs and inconsistent management of this population. The absence of clearly defined and agreed-upon clinical treatment guidelines — and a general lack of processes for assessing and utilizing data related to hemophilia programs — has further hampered efforts to improve patient outcomes. Establishing consensus among stakeholders regarding care coordination and metrics would be a meaningful first step in improving patient management and clinical outcomes, while helping to more effectively address the significant costs associated with hemophilia management.

Hemophilia Treatment

Hemophilia occurs in approximately one in every 5,000 male births, affecting an estimated 20,000 males in the United States.[3] Approximately two-thirds of patients with hemophilia have a family history of the blood disorder, with most cases of hemophilia diagnosed by 3 years of age.[4] Hemophilia patients may experience spontaneous bleeding due to partial or complete deficiencies of coagulation factors. Approximately 80 percent of patients have hemophilia A, or classic hemophilia, which is caused by clotting factor VIII deficiency.[5] Hemophilia B, or Christmas disease, is the result of clotting factor IX deficiency.[3]

Hemophilia cases are classified as mild, moderate, or severe depending upon the extent of the coagulation factor deficiency, with approximately 60 percent of cases categorized as severe.[6] Depending on the severity of the hemophilia, patients may experience musculoskeletal system (muscles and large joints) bleeding; cranial bleeding, which may result in seizures and paralysis; or possibly death, if bleeding is uncontrolled or occurs in a vital organ.[3] Other complications of hemophilia include heart disease, renal disease, and obesity, all of which contribute to poor clinical outcomes and quality of life.[3,4]

Intravenous injection of clotting factor concentrate, known as factor replacement therapy (FRT), is the standard treatment for hemophilia.[3] The factor VIII or factor IX concentrates are either genetically engineered recombinant products or derived from human plasma. FRT is administered two to three



times a week prophylactically,[7] or may be administered in response to an acute bleeding episode, referred to as on-demand therapy. FRT begins early in the life of hemophilia patients and continues into adulthood to avoid repeated hemarthroses that lead to arthropathy.[8]

Approximately 15 to 20 percent of hemophilia patients develop antibodies, or inhibitors, directed against factor VIII or factor IX replacement treatments.[3] Inhibitors develop more commonly in severe hemophilia A patients.[8] Other risk factors that may influence the development of inhibitors include age, race/ethnicity, frequency and amount of FRT treatment, family history of developing inhibitors, type of factor treatment product, and the presence of other immune disorders.[9] Patients with inhibitors are more difficult to treat and experience increased morbidity and mortality.[3,8-11] Current treatment options include high-dose clotting factor concentrates, bypassing agents, and immune tolerance induction (ITI) therapy.[9]

The U.S. Hemophilia Market: Split into 3 Segments

Many new hemophilia therapies are being developed that offer improvements over first-generation or recombinant factor replacements that contain animal and/or human plasma–derived proteins in the cell culture medium and in the final formulation. Second-generation therapies (e.g., Kogenate® FS, Helixate® FS) contain animal and/or human plasma–derived proteins in the cell culture medium, but these proteins are not present in the final formulations. Third-generation therapies (e.g., Advate™, Xyntha®, Eloctate™, Novoeight®) contain no animal and/or human plasma–derived proteins in either the cell culture medium or the final formulations.

The FDA recently approved Biogen's Eloctate for the control and prevention of bleeding episodes, surgical management, and routine preventive treatment in patients with hemophilia A.[12] Eloctate was designed to keep the infused clotting factor in the body longer, thereby allowing for longer intervals between doses.[12] Eloctate is the only treatment for hemophilia A that reduces the frequency of preventive infusions to every three to five days.[12] In addition, the FDA recently approved Biogen's Alprolix® for the treatment of patients with hemophilia B.[13] Alprolix is the first product approved for the treatment of hemophilia B in which the patient will require less-frequent injections in the prevention and reduction of bleeding episodes.[13]

Payor Strategies

Hemophilia is one of the most expensive chronic diseases in the United States, with costs often exceeding $1 million per patient annually.[10,11] The expense of treating this patient population is associated not only with the cost of the medications, but also with assuring timely access to treatments and clinical management, as well as the costs associated with drug administration. If any aspect of this care continuum is disrupted, patients are at risk of complications and poor clinical outcomes, often resulting in additional medical expenses. The cost of factor therapy alone can be hundreds of thousands of dollars, and is higher in patients with more severe disease, such as those with higher rates of bleeding and individuals that have developed inhibitors. All of these elements contribute to greater overall treatment expense.[11]

Payors are tasked with providing timely access to treatments that meet the unique care requirements of each hemophilia patient while attempting to control costs. Adding to the complexity of managing this population is the need to accomplish this in the absence of consensus treatment guidelines, making hemophilia a complex disease-management challenge.[11] Hemophilia is a lifelong disease, and the patient's needs will change over time. A newly diagnosed baby, for example, with no family history of hemophilia, needs extensive nursing and caregiver support until the family can sufficiently self-infuse. As patients learn to self-infuse, the nursing and caregiver burden will decrease.

Approximately one-third of individuals with hemophilia are covered through state Medicaid programs, which are increasingly turning to managed care–based plans to guide care and treatment for beneficiaries with hemophilia.[11] In many cases, these payors do not have medical policies in place that include treatment protocols to manage bleeding disorders. In managing hemophilia patients, payors may contract with specialty pharmacies, hemophilia treatment centers (HTCs), hospitals with 340B pharmacies, or home care/home infusion programs to support the clinical management, appropriate dosing, and distribution of FRT. In many cases, definitive clinical treatment protocols are not in place. Existing protocols are often focused on logistical considerations, such as assuring access to factor products and waste management, rather than defining a clinical approach to the management of hemophilia. Payor treatment strategies do not typically include a framework to focus on clinical matters, such as establishing a requirement for prophylactic versus on-demand FRT, the management of comorbidities, the added risk of coinfection with human immunodeficiency virus (HIV), or outlining an approach for times when surgery is necessary. The lack of policies regarding the clinical care of hemophilia patients has led to inconsistent care. While allowing flexibility and permitting the customization of care based on individual patient needs, the current system may contribute to suboptimal patient out-

Existing protocols are often focused on logistical considerations, such as assuring access to factor products and waste management, rather than defining a clinical approach to the management of hemophilia.

comes and rising costs due to a lack of alignment of goals and strategies to manage this patient population.

Payors remain well-informed about new therapies by relying on specialty pharmacies and pharmaceutical manufacturers for updates regarding availability of new products. However, in the absence of clear consensus treatment guidelines for hemophilia, there are few strategies regarding coverage, formulary approaches for existing therapies, or policies for the management of new bleeding disorder treatments. The nature of hemophilia along with the absence of consensus treatment guidelines detailing best practices are factors that contribute to the significant pharmacy expense associated with managing hemophilia.[11] Further adding to the complexity is the necessity of treatment continuity, or assuring that patients will always have access to the specific FRT that they are being treated with, because FRTs are not interchangeable. Blanket medical policies for substitution of hemophilia treatments are unrealistic, because replacing a recombinant or plasma-based product with an alternative may result in an allergic reaction or lead to inhibitor formation that negatively impacts patient health and increases health care costs.[11] These factors demonstrate the importance and complexity of correctly managing hemophilia; given the long list of competing payor priorities, this often gets lost in the mix.

Payor management of hemophilia treatment may, in some situations, include clinical programs designed to assess the need for treatment and monitor progress. However, as stated previously, they are more often focused on logistics related to minimizing waste, access to treatments, and establishing guidelines for drug distribution. Specific payor strategies for containing hemophilia costs may include:

- Restricted distribution, including home care, the use of home infusion providers, or specialty pharmacy distribution
- Closed provider networks, or limiting prescriptive authority to specialists
- Medical or formulary management policies governing access to therapies; may include copay differentials, preferred therapeutic agents, step therapy, prior-authorization requirements, or nonformulary designation for some treatments
- Waste management programs focused on matching the dosing requirements for hemophilia factor in each patient to the factor replacement products
- Clinical programs to monitor progress

With an emphasis on managing the distribution of hemophilia treatments, payors do not routinely assess differences in the cost and quality of care provided through the various approaches to hemophilia treatment. For example, there is little reported awareness among payors of differences in clinical outcomes for patients cared for within HTCs, through a home care resource, in provider offices, or in the hospital setting. There is a potential knowledge gap as information about factor utilization, the number of patient bleeds, complications, costs, timeliness of service, results of assay testing, and the use of other inpatient services can be collected and interpreted.[11] This information could be of value in allowing payors to anticipate unique patient needs, and be applied in a manner that contributes to improved care in the management of patients with hemophilia.[11]

Provider Strategies

Physicians and other care providers (such as HTCs) that have clinical programs in place to manage hemophilia have been shown to reduce mortality and hospitalization rates.[1,2] The strategies employed within these practices can vary significantly from the programs used by payors. This is primarily due to the focus of HTCs and physicians on patient-specific strategies for care coordination and management, versus the payor focus on access to medications and the processes involved in managing the distribution of drug therapies.

Many tools and resources are used by providers to manage individual patients and, to some extent, the economic aspects of medication use for hemophilia. These may include assay management programs, clinical programs, and dose optimization programs. Providers typically have protocols in place to support the management of hemophilia and have access to information supporting the consideration of other patient-specific factors or conditions (e.g., comorbidities, coinfection with HIV or HCV, or surgical history). Typically, physicians and HTCs are also equipped to make treatment decisions regarding prophylactic versus on-demand FRT based on individual patient history, such as the number of bleeds per month, as well as a working knowledge of patient lifestyle/activity level. While guidelines may be in place within a particular provider's office or an HTC, the absence of consensus treatment guidelines allows for great variability in defining and interpreting what would constitute an optimal prophylactic treatment regimen.[14]

Providers may have protocols in place for existing treatments, but they must also have an established process to assess and update treatment protocols when new therapeutic agents are introduced. U.S. Food and Drug Administration (FDA) approval of new therapies and the expansion of indications for therapies during the past two years have presented additional challenges in the hemophilia treatment space. New therapies require the refinement and development of optimal treatment regimens that are capable of being highly individualized.[15] Providers are tasked with updating treatment protocols while continuing to monitor new and existing regimens for long-term efficacy and unanticipated adverse events, and making revisions as appropriate.

Successful management and improved outcomes for hemophilia patients are more likely to occur when hemophilia treatment approaches are a priority embraced by both payors and providers. Effective programs require knowledge, clinical insight, and the capture and meaningful analysis of clinical data. Additionally, this information must be applied in the treatment setting in a manner that improves patient outcomes and quality of care. Some examples of programs include:

- Prophylactic care programs
- Assay management programs
- Dose optimization programs
- Medical policies or treatment standards
- Clinical programs to monitor progress, assess outcomes, and improve care

These programs are most successful when they are designed with sound clinical objectives and there is effective coordination between the payor and provider. Successful programs are designed to provide coordinated care and involve the patient while supporting education and participation of the patient and family. They are not intended solely to manage the costs associated with the purchase of medications.

Home Care Strategies

Home care providers can be a valuable resource in the management of patients with hemophilia by offering a means for patients to receive in-home infusions of clotting factors either prophylactically or in response to acute bleeds. The nature of services provided by these home care organizations may range from high-touch clinical management to those with a primary focus on distribution. In some instances, home care agencies are affiliates of specialty pharmacies and may be equipped to deliver or administer products, depending on the contractual relationship with the provider or health plan. Organizations with a clinical emphasis can apply treatment protocols and assist with optimizing hemophilia treatments by working with patients, payors, and providers.

State regulations may influence the role played by home care organizations. For example, in some states, HTCs are required to contract with home care providers for the administration of hemophilia treatments. Home care providers can utilize treatment protocols to guide the administration of prophylactic versus on-demand therapy and address other patient-specific considerations, such as the treatment of hemophilia along with other conditions (e.g., comorbidities, coinfection with HIV or HCV, or surgical history).

Similar to HTCs, home care providers are positioned to facilitate the education of patients and family members, and to capture meaningful clinical data to support the optimal management of hemophilia patients, as well as assess the effectiveness of treatments. However, organizations vary widely in the ability to capture and apply this data in a meaningful, patient-specific manner. In the absence of a mechanism for sharing this information with the patient care team, an opportunity for improved care coordination may be lost.

Patient-Centered Strategies

In addition to an emphasis on cost management, patient engagement is crucial in improving clinical outcomes in hemophilia treatment. Payors, providers, and home care organizations that focus on engaging patients in self-management and decision making help ensure improved quality of life.[10] Strategies for patient-centered hemophilia care include[11]:

- Use of best practices, experienced providers, and management programs
- Engagement with hemophilia patient advocacy organizations
- Educational support of patients and family members
- Communication about care management options and decision making
- Data sharing on clinical quality and patient experience

Opportunities for Improvement

The current payor, provider, and home care environment that focuses primarily on the management of reimbursement and distribution contributes to a disorganized approach to managing hemophilia. Competition for patients and the corresponding finances may play against the cost-control objectives of payors and undermine a patient-centered focus in treating those with hemophilia. This results in missed opportunities for coordination of care, integration of services, and improved clinical outcomes.

Despite differences in the implementation of programs and approaches to managing outcomes, stakeholders share many of the same objectives. Increased physician support represents one area where stakeholders have identified a common need. For example, a physician support program that provides education regarding current treatment guidelines, incentives to improve quality of care, and communication about patient-related barriers to care would benefit all stakeholders. Development of comprehensive patient support programs is another potential area for stakeholder collaboration. Components of patient programs may include patient engagement incentives, discussion of barriers to care, adherence support, lifestyle education, and medication review. Third-party support from pharmaceutical manufacturers may also be able to assist providers in improving hemophilia management by providing patient education materials and supporting the education of providers and staff regarding new and emerging treatments. Other assistance might include funding for outcomes-related projects, including risk- or outcomes-based contracts on specific products, waste management programs, and initiatives to facilitate collaboration among stakeholders.

A shift from the current reimbursement-centered strategies toward patient-centered, cost-effective hemophilia management will also require payors and providers to integrate clinical data collection and assessment into the development of evidence-based clinical guidelines. Creating opportunities for the sharing of information and reaching a consensus among stakeholders regarding metrics are key aspects of attaining the goals of better management of hemophilia.

Moving forward, stakeholders must work toward defining mutual, patient-centered treatment objectives that support clinical and financial goals in the effective management of hemophilia patients. These objectives must include strategies for the evaluation and management of meaningful data, logistical and practical considerations related to product distribution, and regulatory issues such as laws regulating product distribution. The primary objective of a more comprehensive and coordinated approach in the treatment of patients with hemophilia is to effectively improve clinical outcomes while managing cost.

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References

1. Soucie JM, Nuss R, Evatt B, et al. Mortality among males with hemophilia: Relations with source of medical care. *Blood*. 2000;96(2):437-442.
2. Soucie JM, Symons J, Evatt B, et al. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia*. 2001;7(2):198-206.
3. Hemophilia Facts page. Centers for Disease Control and Prevention website. **www.cdc.gov/ncbddd/hemophilia/facts.html.** Accessed April 7, 2015.
4. Hemophilia Data & Statistics page. Centers for Disease Control and Prevention website. **www.cdc.gov/ncbddd/hemophilia/data.html.** Accessed April 7, 2015.
5. Hemophilia A page. National Hemophilia Foundation website. **www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A.** Accessed April 7, 2015.
6. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-e47.
7. Blanchette VS. Prophylaxis in the haemophilia population. *Haemophilia*. 2010;16(Suppl 5):181-188.
8. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. *J Blood Med*. 2014;5:207-218.
9. Hemophilia Inhibitors page. Centers for Disease Control and Prevention website. **www.cdc.gov/ncbddd/hemophilia/inhibitors.html.** Accessed April 7, 2015.
10. Dalton DR. Hemophilia in the managed care setting. *Am J Manag Care*. 2015;21:S123-S130.
11. Medicaid Health Plans of America. Addressing the needs of members with hemophilia in Medicaid managed care: Issues and implications for health plans. **www.mhpa.org/_upload/MHPA%20Hemophilia%20Issue%20Brief%20final%20082113.pdf.** July 2013. Accessed April 7, 2015.
12. FDA approves Biogen's Eloctate for hemophilia A. National Hemophilia Foundation website. **www.hemophilia.org/Newsroom/Industry-News/FDA-Approves-Biogens-ELOCTATE-for-Hemophilia-A.** June 11, 2014. Accessed June 1, 2015.
13. FDA approves first long-acting recombinant coagulation factor IX concentrate for patients with hemophilia B. U.S. Food and Drug Administration. News release. March 28, 2014. **www.fda.gov/newsevents/newsroom/pressannouncements/ucm391037.htm.** Accessed June 1, 2015.
14. Ragni MV, Fogarty PJ, Josephson NC, et al. Survey of current prophylaxis practices and bleeding characteristics of children with severe haemophilia A in U.S. haemophilia treatment centres. *Haemophilia*. 2012;18(1):63-68.
15. Bauer KA. Current challenges in the management of hemophilia. *Am J Manag Care*. 2015;21:S112-S122.

Promoting Cost-Effective Sites of Care: Payor Perspectives and Strategies

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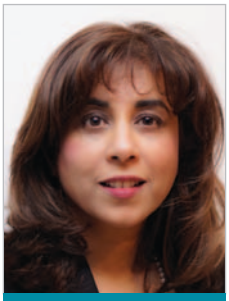
Site of Care Trends and Economic Burden to Plans



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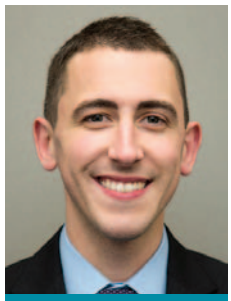

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Managing utilization and reimbursement of pharmaceuticals under the medical benefit is often a challenge for managed care organizations (MCOs) and employer groups. Variances in reimbursement by site of care (SOC) are a major contributor and lead to a substantial disparity in cost for certain infused medications without a correlation to improved outcomes. It is generally understood within managed care that hospital outpatient administration of intravenous pharmaceuticals is drastically more costly than alternative sites of care, including physician offices, freestanding infusion clinics (FSICs), and home infusion services. Although health plans can theoretically generate substantial savings opportunities by promoting the use of cost-effective SOCs, interventions designed to optimize this potential have been relatively limited.

Unfortunately, expensive hospital outpatient utilization of infused pharmaceuticals has been increasing over the last several years. One analysis of health plan medical claims data representing more than 10 million covered lives across all sites of service evaluated the change in site of care expenditure since 2010.[1] Expectedly, the per-member per-month (PMPM) cost of each site of service increased in the four-year time frame of this analysis; however, the hospital outpatient expense grew at a much higher rate (see Figure 1).[1] This increased cost is further put into perspective by the percent of members utilizing these various SOCs. Although the PMPM for hospital outpatient utilization is 40 percent higher than that of physician offices, twice as many patients are receiving care in the physician outpatient setting (see Figure 2).[1] This further demonstrates the disproportionate reimbursement that is provided to hospital outpatient facilities.

The same report also analyzed the utilization and cost of individual products within various sites of care. When aggregating the total cost of the top 10 infused drugs and segmenting these costs by site of care, the average hospital outpatient cost was 96 percent higher when compared with physician office administration.[1] These products, as seen in Figure 3, are primarily for oncology, oncology support, and biologics for autoimmune diseases, including rheumatoid arthritis, Crohn's disease, psoriasis, and multiple sclerosis.[1] Oncology

Figure 1: Medical Pharmacy Allowed Amount PMPM for Commercially Insured Patients by Site of Service, 2010–2013[1]

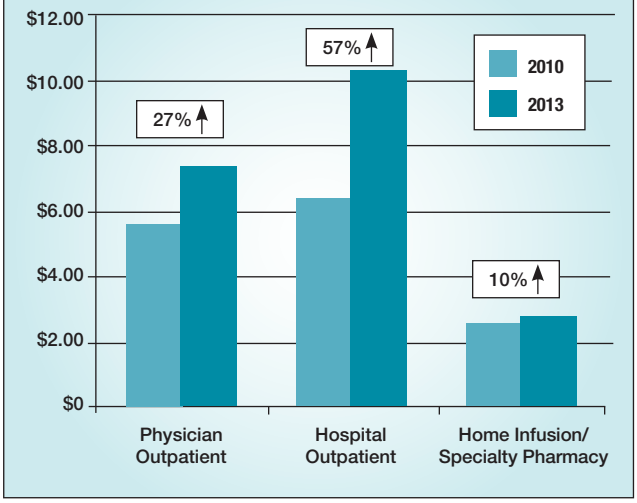
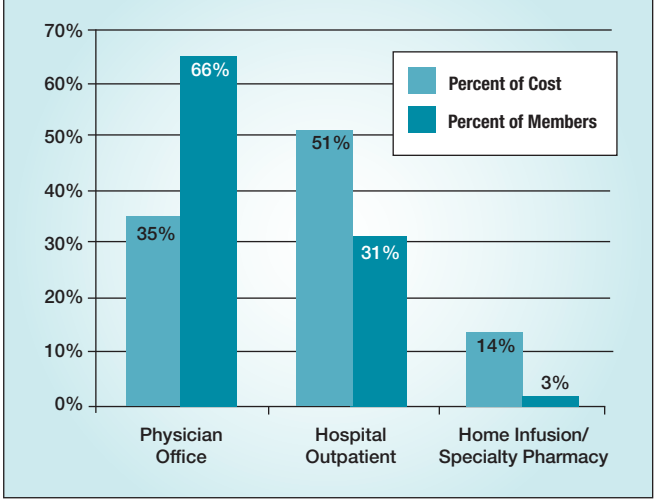


Figure 2: Difference Between Percent of Allowed Amount and Percent of Members Utilizing Various Sites of Care in 2013 (Commercially Insured Patients)[1]



and oncology support medications overall cost nearly 98 percent more in the hospital outpatient setting than in the physician office setting.

It is clear that SOC for infusion services is shifting from physician offices to hospital outpatient facilities. As the utilization of hospital outpatient facilities continues to increase, it places a greater cost burden on MCOs, as well as employer groups. A large burden is being placed on employer groups in particular, as increased cost is associated with various SOCs; in turn, this is reflected in the total cost associated with increased premiums. Additionally, the increase in hospital outpatient utilization has not been associated with improvements in clinical outcomes. Therefore, optimizing cost-effective SOC utilization is a priority for many MCOs and employer groups across the country.

Market Dynamics Leading to Increased Hospital Outpatient Utilization

Before solutions to the SOC challenges in the U.S. health care system can be developed, it is important to understand the reasons for increased hospital outpatient utilization. It is generally accepted that the primary reason for increased cost (cost per claim or cost per unit) within hospital outpatient facilities is related to the current contractual arrangements between the payor organizations and the hospitals. However, this does not explain the increased percentage of patients being referred to these facilities.

There are several market dynamics that have led to increased utilization of hospital outpatient services. One of the most prominent is the acquisition of independent physician practices and physician groups by hospital systems. Hospitals are focusing on purchasing independent practices across multiple specialties as a strategy to build and maintain a competitive advantage, recruit high-quality physicians, and form accountable care organizations. As independent practices become rolled up under hospital systems, referral protocols and billing practices tend to change, leading to more claims billed under the hospital umbrella.

In addition to hospital acquisition of independent practices, there are several physician-related reasons for the trend of increased hospital outpatient utilization. Many physicians are unequipped to administer infusions within their practice. Unfortunately, in this situation, physicians will primarily refer patients to hospital outpatient infusion clinics. This may be derived from a reluctance to refer to a competing physician practice, or a lack of knowledge regarding alternative SOCs, such as FSICs or home care services. Many physicians also credit reduced reimbursement for infusion services as a reason for referring patients to hospital facilities. For many physicians, infusions provided a revenue stream for their practices; however, reduced reimbursement from managed care organizations and employer groups has made some physicians re-examine the profitability and sustainability of infusion services in certain populations. When some physicians feel that it is no longer cost-effective to infuse certain patients, then these patients typically get referred to hospital facilities.

Home infusion services may provide one opportunity for managed care organizations and employer groups to

Figure 3: Commercial Cost per Claim for Top Drugs by Provider Type and Indexed to ASP in 2013[1]

		COST/CLAIM			ASP INDEX (4Q13)		
Provider Type		Hospital Outpatient Facility	Home Infusion/ Specialty Pharmacy	Physician Office	Hospital Outpatient Facility	Home Infusion/ Specialty Pharmacy	Physician Office
HCPCS Code	Brand Name						
J0897	Xgeva®/Prolia®	$3,504	$849	$1,437	2.48	1.07	1.13
J1569	Gammagard Liquid®	$6,590	$3,813	$5,368	2.41	1.29	2.10
J1745	Remicade®	$8,182	$4,393	$3,772	3.00	1.26	1.13
J2323	Tysabri®	$6,156	$4,050	$4,167	1.72	1.12	1.18
J2505	Neulasta®	$6,894	$4,160	$3,402	2.05	1.41	1.16
J9035	Avastin®	$8,745	$5,853	$4,120	2.31	1.20	1.11
J9041	Velcade®	$2,282	–	$1,619	2.02	–	1.15
J9305	Alimta®	$9,109	–	$5,815	2.10	–	1.12
J9310	Rituxan®	$9,434	$11,608	$5,647	2.10	0.71	1.12
J9355	Herceptin®	$5,406	–	$2,867	1.75	–	1.11

offer highly convenient infusion services while simultaneously supporting cost-saving efforts. The utilization of home infusion care allows patients who require regular treatments to receive this treatment in the comfort of their own homes. Home infusion therapy incorporates medications and a trained nursing staff to care for the patient within their place of residence. This accommodation has gained support from the public, since patients who require weekly treatments may have mobility or transportation issues. Home infusions are seen as a way to further allow patient access, while minimizing hospital time and resuming lifestyle activities more rapidly.

In addition, when evaluating the difference between hospital outpatient and home infusion costs, home infusion is significantly less expensive. When looking at the cost of the top 10 infused drugs for commercial lines of business, the cost was over 104 percent more expensive in hospital outpatient facilities when compared with home infusion providers.[1] However, it is important to note that home infusions may not be appropriate for all infusion therapy, specifically if there is a high risk of severe reactions, such as anaphylaxis. Home infusion services can, in the right situations, be cost-effective and more convenient for the member, completely removing the need to travel for infusion services.

Furthermore, many health plan benefits support the use of home infusion services at a reduced financial liability. The member out-of-pocket costs in each SOC can vary depending on the benefit design. Payors can help by structuring the benefit design to incentivize the member to utilize home infusion services. It is possible that this may also demonstrate a positive impact on patient adherence.

In addition, billing and coding continues to be a problem when submitting claims for reimbursement. Specialty medications should be billed as units of service, reflecting the vial and dosage. The Centers for Medicare & Medicaid Services conducted an audit on medical claims and overpayments, utilizing Noridian as one of the Medicare contractors to conduct the audit within their jurisdiction. Several instances of miscoding and incorrect billing resulting in large overpayments were cited in the report. For example, one provider had administered 30,000 and 40,000 milligrams of Gamunex® to two patients and billed for 1,600 units of service (which equates to 800,000 milligrams) and 3,200 units of service (which equates to 1,600,000 milligrams).[2] Using the correct code, the number of units that should have been billed for 30,000 and 40,000 milligrams was 60 and 80, respectively.[2] Therefore, it was found that the Medicare contractor paid the provider $176,738 when they should have paid $4,175, translating to an overpayment of $172,563.[2] It was also discovered that there was a considerable number of claims — 299 line items, specifically — that displayed a combination of the incorrect number of units of service and incorrect Healthcare Common Procedure Coding System (HCPCS) code.[2] These errors resulted in overpayments of $746,895.[2] Therefore, it is crucial that billing and coding be closely monitored in order to reduce errors and contain unnecessary costs.

There are also patient-related reasons for increased hospital outpatient utilization. Most patients have a very limited understanding of different SOCs. Patients tend to follow the recommendations of their physicians and are not aware of other alternatives, such as the possibility of home infusion. Patient out-of-pocket cost also has the potential to drive utilization to hospital facilities. Patients may have a lower financial responsibility when receiving care from hospital facilities compared with some of the alternative SOCs.

Although hospital outpatient facilities are generally more costly, it is important to remember that this is still largely considered a safer option by many physicians. If a patient presents a complicated case or has a risk of adverse reaction, many physicians feel more comfortable with these patients receiving care in a hospital setting. Therefore, if a physician has safety concerns regarding a specific patient, it may be challenging to transition that patient away from a hospital outpatient setting.

Using Medical and Pharmacy Data to Evaluate Opportunities

Before designing an initiative to optimize the use of cost-effective SOCs, it is essential to have an accurate understanding of what factors are driving the utilization of certain products into the various sites. Additionally, it is important to have a realistic perception of the true economic opportunity that exists for each product or class of products being targeted. Not only will this help identify specific patient subsets or indications to include in SOC initiatives, but it will also allow the ability to ensure that the program investment will not outweigh anticipated savings.

To accomplish this, it is important for health plans to take a very strategic look at their medical and pharmacy data. Understanding the PMPM of a certain product at various sites is not enough information to develop informed intervention strategies. SOC utilization should be broken down in multiple ways to determine if specific trends can be identified. These may include:

- Patient diagnosis/indication for use
- Physician specialty
- Patient/physician geography
- Patient out-of-pocket cost
- Physician affiliation status
- Percentage of patients referred per prescriber

These variables can offer insight into the reasons for increased hospital outpatient utilization and help provide direction regarding required interventions that should be considered for a SOC initiative.

A recent analysis of health plan medical and pharmacy claims data was conducted to evaluate factors leading to increased hospital outpatient utilization of Remicade® (infliximab).[3] This analysis was also designed to determine the cost difference between the various sites. The results of the analysis were interesting. A total of 3,161 patients were administered Remicade, representing 17,903 total claims and $88,032,179 in cost.[3] Of the total cost, 55 percent was associated with patients utilizing Remicade to treat a gastrointestinal (GI) condition and 40 percent for patients with a diagnosis of rheumatoid arthritis. Once SOC was segmented for the different indications, it was observed that 67 percent of GI-related cost was derived from hospital outpatient utilization, compared with just 26 percent for rheumatoid arthritis.[3] This analysis also showed a difference in cost per claim of nearly $3,700 between physician office utilization and hospital outpatient facilities.[3]

This example demonstrates how data can help craft strategies for SOC initiatives. Based on this data, health plans may want to focus Remicade SOC initiatives on patients receiving hospital outpatient administration for GI conditions. There may be less opportunity for savings by focusing on patients with rheumatoid arthritis. This analysis

Before designing an initiative to optimize the use of cost-effective SOCs, it is essential to have an accurate understanding of what factors are driving the utilization of certain products into the various sites.

also helps to illustrate the potential savings that could be generated from a SOC initiative. Based on these numbers and within this patient population, every 1 percent of claims that is transitioned to an alternative SOC generates a savings of more than $660,000. Once the potential savings are analyzed, it allows payors to assess the level of investment they are willing to allocate for SOC initiatives.

Strategies MCOs Are Reviewing Based on Patient Need

Many payors are looking at different strategies pertaining to site selection dependent on patient need. The following are some options payors are investigating.

To help provide patients and physicians with education regarding alternative and possibly more convenient SOCs, initiatives are being piloted and researched for member beneficiaries and network providers. In order to support this, referral centers staffed by nurses and benefit coordinators provide patient and physician support and scheduling assistance for the administration of intravenous medications. Although participation with referral centers is not mandatory, it can be designed in such a way as to help relieve some of the administrative burden that is placed on the office staff. The referral center nurses have the ability to engage in informative discussions with members regarding alternative treatment sites and differences in out-of-pocket expenses based on their benefit design. The nurses can also work with members to identify the most convenient option available based on their specific needs and assess whether additional patient support services are required.

Payors are looking at a myriad of other services to assist patients, such as making field calls directly to patients and providers regarding SOC and benefit design, offering real-time benefits information to providers and patients, assisting in determination of the most convenient and lowest-cost site of service for patients, aiding physician offices with navigation through the prior-authorization process, offering drug and disease state education, providing information related to copayment assistance programs, and acting as a concierge service to see the member from initiation of medication through administration of the product.

The intent of such strategies and programs is to offer patients and physician practices a resource to broaden their understanding of alternative sites of care for infusion services, provide administrative support to reduce the burden on offices, and improve patient satisfaction with care.

Conclusion

Infusion services are steadily shifting from physician offices to hospital outpatient facilities, and this trend is not expected to subside in the near future. This is due to a variety of different reasons, but a major aspect is a lack of knowledge regarding alternative SOCs by both patients and providers. As specialty drug costs continue to spiral out of control, it is important for health plans to consider all opportunities for savings. SOC optimization may be one strategy to help contain the escalating specialty spend without sacrificing outcomes. Although very few plans have implemented strategies focusing on the current SOC problem faced by the U.S. health care system, the savings potential has been demonstrated to be substantial. However, it is important to understand the influence of local and physician dynamics on SOC utilization before implementation of any optimization strategies. Additionally, it is essential to have a solid understanding of the true cost-savings potential to make sure the return on investment is worth the effort.

SOC is not an easy problem to correct and the reasons for high hospital outpatient utilization are multifaceted. However, as time progresses and costs continue to escalate, health plans will be unable to ignore their SOC problems moving forward. A long-term priority will have to involve the renegotiation of hospital contracts; this, however, is much easier said than done. In the meantime, health plans will have to be creative in their approaches to site of care optimization and learn from the successes of other organizations.

References

1. Magellan Rx Management. 2014 medical pharmacy trend report™. **www.magellanrxinsights.com.** Accessed June 8, 2015.
2. Office of Inspector General, U.S. Department of Health and Human Services. The Medicare contractors for Jurisdiction E overpaid providers for selected outpatient drugs. **https://oig.hhs.gov/oas/reports/region9/91302009.pdf.** January 2014. Accessed May 1, 2015.
3. Real-world analysis of the economic impact of infliximab utilization by site of care and medical diagnosis within two regional health plans. *Magellan Rx Report.* Fall 2014:31-33.

Reining in Medical Pharmacy Oncology Costs

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Oncology accounts for 5 to 11 percent of all health care spending, with costs related to cancer care rising faster than any other medical specialty.[1,2] In 2010, the United States spent approximately $125 billion in direct medical costs for cancer treatment.[1,2] By 2020, that figure is expected to top $173 billion annually, driven by an aging population, increased cancer survivorship, and the availability of new and potentially expensive biologic drugs, some that are expected to cost upward of $100,000 per year.[1,2] In the past decade, the average monthly cost of a brand-name cancer drug has doubled to $10,000, and insurers and patients are spending more on cancer drugs today than on medications for any other therapeutic area except cardiovascular disease.[3,4]

According to a 2014 IMS report, spending on oncologics and oncology-related supportive care treatments reached $43.4 billion, of which a substantial portion is related to new melanoma, lung, breast, and prostate cancer therapies.[3] The Magellan Rx Management 2014 Medical Pharmacy Trend Report™ notes that oncology and oncolytic support medications represented approximately 52 percent of the medical pharmacy spend in 2013 for commercial members.[5] Similarly, for Medicare members, oncology and oncolytic support medications totaled approximately 60 percent of the medical pharmacy spend in 2013.[5] This cost trend will likely continue, as more than 700 oncology medications are currently in clinical trials or have been submitted for FDA approval.[6] Of these new medications, 80 percent are considered first-in-class.[6]

Influential factors leading to increased oncology-related costs include:

- High drug development costs
- Lack of generic or biosimilar competition
- Political and emotional ramifications of perceived rationing of cancer drugs
- Off-label use
- Financial incentives for physicians to use higher-cost drugs
- Inefficient use of cost-effective sites of care (e.g., physician offices vs. hospital outpatient facilities)[7]

Site of care has emerged as a major cost driver in oncology spending as chemotherapy infusions move from physician office settings to outpatient hospital facilities, driving up reimbursement. This shift is propelled, in part, by consoli-

dation in the industry and the purchase of oncology practices by hospital systems. In the Magellan Rx Management 2014 Medical Pharmacy Trend Report, nearly 60 percent of payors noted that hospital systems in their area were purchasing oncology practices, with 21 percent of payors stating that over 50 percent of oncology practices have already been purchased.[5]

According to IMS Health, administration costs in an outpatient hospital setting are nearly 190 percent higher for brand-name drugs than for those same drugs administered in a physician office.[15] The Magellan Rx Management analysis reported a similar trend, in which the actual cost of outpatient administration was two to three times the average sales price (ASP) when compared with administration in a physician office for commercial plans.[5] Therefore, it is not surprising that 71 percent of payors surveyed in 2014 reported moving specialty infusion to lower-cost sites of service as their top goal in specialty drug management.[16]

With so many contributing factors, it is evident that succeeding in oncology cost management will require a comprehensive specialty drug management strategy that spans benefit design, reimbursement, and utilization. Developing solutions that are designed to eliminate waste, promote appropriate competition, and reduce or prevent complications will provide opportunities to positively impact the specialty cost curve. However, to generate a meaningful level of savings, payors must be willing to implement novel management strategies targeting specific specialty conditions.[7]

Misaligned Incentives and Novel Payment Reform

The current fee-for-service (FFS) payment structure reimburses most oncologists for office-administered drugs based on the medication's ASP plus an additional percentage. According to payor survey responses, the average markup in 2014 was 15 percent, which is an increase of 6.5 percent based upon the 2013 survey responses.[5] This increase in reimbursement could be driven, in part, by the acquisition of small, community-based oncology practices by larger group practices. This creates greater power to negotiate increased reimbursement rates with commercial health plans.[5] The markup on chemotherapy and oncology supportive care products has become a meaningful revenue stream for oncologists across the country. Unfortunately, this reimbursement structure can often result in misaligned incentives and lead physicians to prescribe higher-priced therapies, even though there may not be any additional therapeutic benefit to their patients.[8,9] The federal government has sought to rein in excess costs associated with physician-administered drugs by standardizing reimbursement to ASP plus 6 percent — however, as previous stated, commercial health plans continue to spend significantly more.[10,11]

Treatment variation between oncology practices also contributes to the increased cost of cancer care. A study published in *Health Affairs* in 2015 found an annual difference in Medicare Part B payments of approximately $4,000 per patient for oncology-related costs when comparing high spend to lower spend practices.[12] After assessing the

Table 1 **Proposed Payments Under the American Society of Clinical Oncology's Consolidated Payments for Oncology Care Proposal[13]**

Payment Type	Explanation
New patient payment	Practice receives a single new patient payment that compensates physician and staff time devoted to the initial patient evaluation, treatment planning, and patient education. This replaces CPT-based evaluation and management payments. The costs of any diagnostic testing are still billed and paid separately.
Treatment month payment	Practice receives a single treatment month payment each month the patient receives treatment. This payment replaces all current CPT-based payments for chemotherapy administration, therapeutic injections/infusions, hydration services, and established patient evaluation and management visits. Payments occur if patients are using oral medications or infused/injected drugs.
Active month payment	Practice receives an active monitoring month payment each month the patient is under the active care of the oncology practice but does not receive any cancer treatment during the month.
Transition-of-treatment payment	Practice receives a transition-of-treatment payment each month in addition to either a treatment month payment or an active monitoring month payment. This additional payment reflects the time involved in treatment planning and patient education when significant changes occur in the patient's disease or treatment plan.

consistency of these cost trends over time, the authors suggest the differences were due to practice preferences, not patient preferences.

To eliminate any financial incentive to use higher-priced chemotherapies and to drive evidence-based care, payors are shifting from FFS reimbursement for cancer care to value-based reimbursement models.

The American Society of Clinical Oncology advocated such models in 2014 as part of its Consolidated Payments for Oncology Care proposal (see Table 1).[13] In particular, the organization recommends changing medication reimbursement from ASP plus 6 percent to offering providers a cancer therapy management fee separate from the actual cost of the drug. The group estimates this change could save the Medicare system up to $1 billion within 10 years of implementation, with the potential for even more cost-savings if physician prescribing patterns shifted away from those influenced by self-interest.

The Centers for Medicare & Medicaid Services (CMS) is now considering such models. In April 2015, the CMS Innovation Center accepted letters of intent for its Oncology Care Model (OCM), a multi-payor shared savings model for most cancer types. Under the two-part Medicare FFS OCM plan, participating clinicians will receive a monthly enhanced care management payment of $160 per beneficiary for each six-month episode the patient is under active treatment. All other services will be billed as FFS, but providers will share in any savings resulting from improving care delivery through a performance-based payment.[14]

Magellan Rx Comprehensive Oncology Management

Significant savings, along with favorable clinical outcomes, have been demonstrated through the implementation of medical pharmacy and radiation oncology management programs offered by Magellan Rx Management. These programs utilize a comprehensive approach to oncology management, which includes supporting clients in the development of medical necessity criteria for medical and radiation oncology services. Collectively, over the past 22 years, Magellan has provided oncology management services to 18 different clients, representing 13.5 million lives.

The medical policies and management strategies integrate insights obtained through an extensive analysis of National Comprehensive Cancer Network (NCCN) Guidelines, Clinical Pharmacology, DrugDex, FDA labeling, national/international coverage guidelines, public/peer-reviewed literature, health plan medical pharmacy policies, CMS policies and coverage guidelines, American College of Radiation Oncology (ACRO), American Society for Radiation Oncology (ASTRO), American College of Radiology (ACR), and other compendia sources. In addition to quarterly updates through Therapeutic Assessment and Pharmacy and Therapeutics committees, each of the Magellan Rx Management medical policies is reviewed annually by an oncology advisory panel, which includes:

- Input from practicing oncologists from national cancer centers and community practices
- Review of oncology-related product pipelines, complex case review, and discussion of management strategies and oncology trends
- Strategies to promote best practices and quality of care

An enhanced utilization management and prior-authorization process is a critical component of the Magellan oncology management strategy. This process is based on the highest standards of clinical practice and has resulted in improved quality of care for health plan patients, improved provider satisfaction with evidenced-based and collaborative approaches, and significant plan savings.

Through the Magellan program, providers can also utilize Web-based tools to help improve administrative efficiencies. This includes a comprehensive prior-authorization process that utilizes clinicians as initial-level reviewers, as well as peer-to-peer discussions prior to any adverse determinations. These online tools also provide physician access to detailed patient information and reports regarding the status of both medical and radiation oncology requests.

Another strategy that Magellan Rx Management has implemented for medical pharmacy medications includes the integration of a post service pre-payment claim edit process. This allows for drugs under the medical pharmacy benefit to be managed with the same level of sophistication applied under the pharmacy benefit. Essentially, the submitted claims are reviewed by Magellan Rx Management relative to a rules engine, which:

- Ensures providers are utilizing physician office–billed drugs as per their FDA label and compendia-approved uses
- Validates all diagnosis values for eligible diagnosis
- Edits for maximum units by drug, gender, age, diagnosis, and weight
- Edits for prior authorization (PA) on drugs that require PA

- Eliminates claim submissions with physiologically impossible doses
- Validates loading doses
- Validates drug waste, stopping the routine billing of full vials

One health plan client, covering 2 million lives, experienced significant savings by implementing management of medical benefit drugs, with the majority being oncology agents. The Magellan program included strategies such as provider reimbursement, prior authorization, post service pre-payment claims edits, and utilization shift. This program resulted in annual savings of $41 million.

The Magellan oncology solutions were effectively applied as a targeted approach by another payor client to improve clinical and economic management of multiple myeloma. For this program, Magellan Rx Management is utilizing an integrated strategy that spans across both medical pharmacy and pharmacy benefit oncology medications and is primarily based on NCCN and Mayo Clinic guidelines. Projections for the program feature a savings of $50,000 per treatment cycle for every patient treated in a manner consistent with the Mayo Clinic guidelines. Based on the health plan membership of approximately 700,000 lives, this initiative is estimated to result in a savings of $695,000 annually.

The Magellan Rx Medical Pharmacy Oncology Management program brings additional expertise and solutions to improve quality of care through provider collaboration and ongoing network support. As part of the oncology management program, Magellan has implemented an extensive educational campaign for providers that is specifically designed to reduce unnecessary expenditure without sacrificing patient outcomes. This program highlights equally efficacious and clinically appropriate treatment options, with comparable toxicity profiles, and the cost comparisons of these targeted regimens for certain cancers, focusing on those that may be of optimal value. In addition, engagement with providers through peer-to-peer discussions results in collaborative relationships that promote high-quality and cost-effective care for all patients.

Case management also plays a crucial role in oncology management by identifying patient-specific challenges and customizing support services to best meet the needs of individual patients. Educating patients on their current treatment regimens, therapy expectations, management of adverse reactions and toxicities, identification of depression and referral to behavioral support groups, and providing consultations on palliative care and advanced directives are all key components to a patient-centric approach.

Magellan has integrated a Radiation Oncology Solution to help ensure that the type and amount of services each patient receives during their treatment plan are clinically relevant, and to initiate a shift to less-costly radiation therapies when indicated. Magellan utilizes its data in order to customize a solution for each health plan, and promotes the most appropriate use of modalities when delivering radiation therapy based on the treatment algorithm and national clinical guidelines. Peer-to-peer consultations are provided with Magellan radiation oncologists as part of the program.

As an example, one plan realized its radiation therapy costs were escalating, and in response, Magellan developed an educational initiative for providers when ordering these services for patients. Magellan provided on-site and web-based training for physicians, disseminated educational materials, and facilitated collaborative discussions pertaining to clinical rationale. The results led to the development of the following resources for this specific program: a list of Current Procedural Technology (CPT) codes requiring prior authorization, cancer site checklists, evidence-based clinical cancer guidelines by diagnosis, an outpatient radiation therapy billable CPT codes claim resolution matrix, and a radiation oncology utilization quick reference guide. In addition, a document addressing frequently asked questions for medical oncologists, radiation oncologists, and cancer treatment facilities was included. This program has received a positive response from the plan and its oncologists. Physicians stated that transparency, flexibility, and clinical expertise were the top three program attributes that differentiate the Magellan program from any other program.

Genetic testing is also part of the utilization management process for both medical and radiation services, which includes consultation provided by genetic specialists on equivocal and complex results. In addition, genetic counseling is given to patients who have predictive genomic testing performed. These components allow for improved patient care with targeted, cost-effective tests and therapeutic options, while reducing the avoidance of inappropriate testing or unproven therapies.

A cancer diagnosis not only affects the individual, but also affects the caregivers. Magellan also believes in the significance of considering the caregiver by offering a successful combination of technology, care management, and focused interventions directly to caregivers who are supporting this patient population. Once a caregiver is identi-

fied, focused outreach is conducted to avert mental and physical health concerns. Interventions are integrated to help minimize any distress and dysfunction that a caregiver may experience, in order for them to receive the care and support they may need.

Magellan continues to evaluate new and innovative opportunities to improve patient outcomes and help contain the escalating cost of cancer care for their health plan clients. Unfortunately, this is not a one-size-fits-all approach, and each plan will have to evaluate what strategies are appropriate for their patients and network providers. However, with oncology costs expected to increase, the importance of implementing novel solutions has never been greater.

Benefit Concerns

The largest majority of oncology drugs — with the exception of some oral medications and a few self-injectables — fall under the medical benefit. This makes it difficult for payors to track actual utilization and cost, thus limiting their efforts to ensure the medications are used appropriately.[7,10] In fact, just 59 percent of self-insured employers even receive reports on specialty drug utilization (oncology and other drugs) under the medical benefit, compared with 83 percent who receive reports pertaining to spending under the pharmacy benefit.[16] This represents a significant knowledge gap.

Payors are divided on the financial impact of integrating medical and pharmacy benefits. The Magellan Rx Management survey found that more than half of payors without member contribution parity requirements in place during 2014 estimated members would fare better if drugs were billed through their medical benefit, while one-third of health plans estimated out-of-pocket costs for members would be lower if the drugs were billed through their pharmacy benefit. This highlights the continuing need for more unified and consistent specialty drug management across pharmacy and medical benefits.[5]

Searching for Other Options

Nothing is off the table when it comes to controlling the high cost of cancer drugs. Examples of the current management strategies being deployed are[17]:

- Evidence-based prior-authorization strategies
- Programs to improve patient adherence with recommended therapies
- Restricting the use of third-line therapies with limited clinical value
- Clinical programs which limit prescribing to approved labeling, and require appropriate testing when warranted, such as genetic tests or markers
- Providing palliative care/end-of-life programs

Within the next decade, the majority of cancer medications will most likely be highly targeted and costly specialty drugs, with many treatments exceeding $100,000 a year. As payors attempt to manage this increasingly high-priority therapeutic area, it will be essential to ensure that these drugs are used for the appropriate patients — according to evidence-based clinical treatment guidelines — and administered in the most cost-effective treatment settings.

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References

1. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-128.
2. Guy GP, Jr., Ekwueme DU, Yabroff KR, et al. Economic burden of cancer survivorship among adults in the United States. *J Clin Oncol*. 2013;31(30):3749-3757.
3. IMS Institute for Healthcare Informatics. Medicines use and spending shifts: A review of the use of medicines in the U.S. in 2014. April 2015.
4. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med*. 2011;364(21):2060-2065.
5. Magellan Rx Management. 2014 medical pharmacy trend report. **www.magellanrxinsights.com.**
6. Pharmaceutical Research and Manufacturers Association of America. Nearly 800 medicines and vaccines in clinical testing for cancer offer new hope to patients. 2014.
7. Lotvin AM, Shrank WH, Singh SC, et al. Specialty medications: Traditional and novel tools can address rising spending on these costly drugs. *Health Aff (Millwood)*. 2014;33(10):1736-1744.
8. Towle EL, Barr TR, Senese JL. The national practice benchmark for oncology, 2013 report on 2012 data. *J Oncol Pract*. 2013;9(6s):20s-38s.
9. Jacobson M, O'Malley AJ, Earle CC, et al. Does reimbursement influence chemotherapy treatment for cancer patients? *Health Aff (Millwood)*. 2006;25(2):437-443.
10. Hornbrook MC, Malin J, Weeks JC, et al. Did changes in drug reimbursement after the Medicare Modernization Act affect chemotherapy prescribing? *J Clin Oncol*. 2014;32(36):4042-4049.
11. Jacobson M, Earle CC, Price M, et al. How Medicare's payment cuts for cancer chemotherapy drugs changed patterns of treatment. *Health Aff (Millwood)*. 2010;29(7):1391-1399.
12. Clough JD, Patel K, Riley GF, et al. Wide variation in payments for medicare beneficiary oncology services suggests room for practice-level improvement. *Health Aff (Millwood)*. 2015;34(4):601-608.
13. American Society of Clinical Oncology. Consolidated payments for oncology care: Payment reform to support patient-centered care for cancer. May 2014.
14. Oncology Care Model page. Centers for Medicare & Medicaid Services website. **http://innovation.cms.gov/initiatives/Oncology-Care.** Accessed April 23, 2015.
15. IMS Institute for Healthcare Informatics. Innovation in cancer care and implications for health systems: Global oncology trend report. May 2014.
16. EMD Serono. EMD Serono specialty digest™, 11th edition: Managed care strategies for specialty pharmaceuticals. **http://specialtydigest.emdserono.com/Digest.aspx.** Accessed June 29, 2015.
17. Greenapple R. Rapid expansion of new oncology care delivery payment models: Results from a payer survey. *Am Health Drug Benefits*. 2013;6(5):249-256.

Novel Oral Anticoagulants for Nonvalvular Atrial Fibrillation: Evaluating the Evidence and the Cost

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Approximately 2.7 million to 6.2 million American adults are afflicted with atrial fibrillation (AF), a population that is expected to double over the next 25 years.[1] Hospitalizations of patients with AF indicated as the primary diagnosis are greater than 467,000 annually, and more than 99,000 deaths are attributed to AF per year.[1] In addition, it is also estimated that treatment of AF patients costs $26 billion in the United States annually, and this cost burden is expected to rise.[1]

AF is associated with a fivefold increased risk for stroke, contributing to more than 15 percent of all strokes in the United States; a threefold increased risk for heart failure (HF); and a twofold increased risk for both dementia and mortality.[1,2] Research indicates that strokes in individuals with AF are more severe and costly than those in patients without AF.[3,4] This is likely due to the fact that strokes in patients with AF are associated with an increased risk for heart failure, dementia, and all-cause mortality.[1,5,6]

With an aging population in the United States, the incidence of AF and the associated costs will continue to rise.[7,9] Patients with AF are hospitalized twice as often as patients without AF and are three times more likely to incur multiple hospital admissions.[1] This observation is demonstrated by studies that found hospitalization rates were 23 percent higher between 2000 and 2010, in patients with AF who were ages 65 and older.[8]

The association of AF with an increased likelihood of stroke will have meaningful financial consequences. An analysis of direct health care costs assessed on a per-member per-month (PMPM) basis for patients with stroke demonstrated that costs rose by 24 percent after the diagnosis of AF was made.[5,10]

Collectively, this information raises significant clinical and financial concerns regarding the successful treatment of AF and makes nonvalvular atrial fibrillation (NVAF), in particular, a critical management priority for health plans.

Management of Atrial Fibrillation

Treatment guidelines from the United States, Canada, and Europe recommend the long-term use of oral anticoagulants to reduce the risk for stroke in patients with NVAF who have no contraindications and who have a moderate-to-high risk for stroke based on the $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Prior Stroke or TIA or Thromboembolism [doubled]) or CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes Mellitus, Prior Stroke or TIA or Thromboembolism [doubled],

Vascular disease, Age 65 to 74 years, Sex category).[11-13] Table 1 highlights current guidelines.

Warfarin has been the gold standard for oral anticoagulation for more than 50 years. Previous studies have found a 62 percent improvement in primary and secondary stroke prevention versus placebo in patients with AF who are taking warfarin.[14] However, for some patients, warfarin therapy involves several challenges, including[14]:

- The need for frequent international normalized ratio (INR) monitoring
- Dietary restrictions
- Drug-drug interactions[15]

From a clinical perspective, the primary challenge associated with the management of patients on warfarin is that many spend a significant time out of the ideal INR range. Management of these patients can be difficult, requiring frequent dose modifications, and is accompanied by the likelihood of higher medical costs related to an increased rate of complications.[16]

The challenges of managing warfarin therapy, along with the often symptomless nature of AF, contribute to significant rates of nonadherence to therapy amongst these patients. One longitudinal study found only two-thirds of patients with AF were taking warfarin 30 months following their diagnosis.[17] Another study, conducted at an anticoagulation clinic, determined patients were nonadherent about one-fifth of the time.[18]

Not surprisingly, nonadherence results in higher medical costs. Casciano et al evaluated claims from 13,289 patients with NVAF for whom warfarin was prescribed. Of these, 40 percent of patients were determined to be adherent. Of importance, inpatient admissions and emergency department visits were lower amongst adherent patients. This, in turn, resulted in significantly lower overall medical costs despite higher pharmacy and outpatient costs.[19]

Greater Adherence with Novel Oral Anticoagulants?

Experts are hopeful that adherence will improve with the novel oral anticoagulants (NOACs). One feature of NOACs is that these agents require significantly fewer dose adjustments and less routine monitoring, while affording patients greater flexibility with regard to their diets. The demonstration of adherence to these therapies in practice will be critical. A 2013 study based on claims data from 17,691 AF patients who filled prescriptions for either dabigatran or warfarin found that 39 percent of the 7,062 patients in the dabigatran cohort did not continue the drug for the six-month duration of the study, with an average time to discontinuation of approximately two months.[20] Of those patients who stopped taking dabigatran, a large percentage subsequently initiated warfarin, with a mean time to initiation of approximately two months.[20]

Another study evaluated a cohort of 5,376 patients with NVAF who started therapy with dabigatran and found that nearly one third demonstrated poor adherence (proportion of days covered [PDC], 80 percent).[21] Lower adherence was associated with increased risk for combined all-cause mortality and stroke. The study concluded that despite the potential ease of use, there must be concerted efforts to optimize adherence to NOACs in order to improve clinical outcomes.[21]

Given rates of nonadherence as high as 50 percent with most cardiovascular drugs, Hugo ten Cate, having conducted research at the Cardiovascular Research Institute in Maastricht, the Netherlands, wrote the following in a publication discussing the issue of adherence to NOACs, relative to traditional anticoagulants: "It can be expected that in the management of NOACs nonadherence may reach comparable figures (±50 percent) if no measures to boost adherence are being taken."[22]

Table 1 Current Guidelines for the Prevention of Thrombotic Events in Patients with NVAF[11-13,23]

Issuing Organization	Indication	Recommendation
European Society of Cardiology[11]	CHA_2DS_2-VASc score ≥1	Oral anticoagulation (NOAC preferred)
Canadian Cardiovascular Society[13]	Most patients ≥65 years old or those with $CHADS_2$ score ≥1	Oral anticoagulation (NOAC preferred)
American College of Cardiology/American Heart Association/ Heart Rhythm Society[12]	Patients with prior stroke, TIA, or CHA_2DS_2-VASc score ≥2	Oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban)*
American College of Chest Physicians[23]	$CHADS_2$ score ≥1	Oral anticoagulation (dabigatran preferred)**

*Edoxaban had not been approved for U.S. market when guidelines released.
**Dabigatran was the only NOAC on U.S. market when guidelines released.

Gaps in Care

Despite unanimous agreement amongst medical societies regarding the clinical benefits of using oral anticoagulant therapy in patients with NVAF, numerous studies find that the condition, overall, is poorly managed.[19,24-28]

For example, about 40 percent of patients do not receive oral anticoagulation as recommended by national guidelines, although studies suggest contraindications to oral anticoagulants are present in only 15 percent of patients with AF.[24-26] Underuse is particularly prevalent in the elderly, primarily because of concerns about the risk of dangerous bleeding.[29] However, this is the very population with the highest risk for stroke.[30] A variety of factors drive the underuse of anticoagulation therapy, including physician preference and concerns about bleeding; patient preference and age; patient health literacy; and access to clinics for INR monitoring.[15]

The economic implications of suboptimal anticoagulation are significant. One study estimated that optimizing oral anticoagulation therapy in half of those already receiving it would save the United States $1.3 billion by preventing strokes and bleeds. It is projected that optimizing therapy in half of the preventive treatment candidates who are currently *not* receiving anticoagulant therapy would save $1.1 billion by preventing strokes.[31]

Can the Novel Oral Anticoagulants Improve Care?

The significant barriers to optimal care with warfarin treatment helped drive the development of the NOACs. Four of these agents are currently approved in the United States for stroke prevention in patients with NVAF: the thrombin inhibitor dabigatran (Pradaxa®), and factor Xa inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa™).

Clinical trials for the four NOACs all demonstrated superiority (dabigatran 150 mg twice-daily dose) or non-inferiority to warfarin in terms of stroke prevention and bleeding risk.[32-35] Also noted was a statistically significant reduced risk of intracranial bleeding with NOACs compared with warfarin.[32-35] Additionally, treatment with apixaban and edoxaban was also associated with a reduction in all-cause mortality compared with warfarin.[34,35] A meta-analysis of four major clinical trials found the NOACs appear safer than warfarin, even in patients with a history of warfarin treatment.[36]

The NOACs have several benefits when compared with warfarin, including a fixed dose, more rapid onset of action, no dietary and few drug-drug interactions, less intracranial bleeding, and a shorter half-life.[37] However, there are also several disadvantages, including twice-daily dosing with dabigatran and apixaban, no method for monitoring of blood levels and adherence, uncertainty as to whether a fixed dose is the best dose, high renal clearance, and cost. They are also not approved for use in patients with valvular AF, in whom they may increase the risk of bleeding and stroke.[22,38]

Until recently, the lack of a reversal agent was also a concern. In March 2015, however, Boehringer Ingelheim filed for FDA approval of the first reversal agent, idarucizumab, for dabigatran.[39] The FDA has granted breakthrough status for this drug.[39] Several other such agents are in late-stage clinical trials for reversal of the effects of other NOACs, with one such drug, andexanet alfa, also having been given breakthrough status.[40,41] While it appears there will be reversal agents readily available for the NOACs in the near future, there is limited pricing information available at this time, making it difficult to determine whether these agents will further encourage the use of the NOACs.

Studies find relatively rapid adoption of the NOACs in clinical practice.[24,42] By mid-2013, an analysis of national medical and prescription claims data of newly diagnosed patients with NVAF from a commercial insurer found that the NOACs dabigatran, rivaroxaban, and apixaban (edoxaban had not yet been approved) accounted for 62 percent of new prescriptions and 98 percent of anticoagulant-related medication costs during the 36-month study period.[43] Rivaroxaban had the greatest market share by June 2013, followed by dabigatran.[43]

The newest entrant into the market, edoxaban, will likely face some challenges in gaining significant uptake into the market as prescribers assess the most appropriate NOAC patient type.[44] The drug comes with a black box warning noting that it is less effective in patients with a creatinine clearance >95 mL/min. In addition, the dosage must be reduced in patients with a creatinine clearance of 15 to 50 mL/min.[45]

Studies evaluating the use of NOACs in real-world practice settings suggest that the drugs are being prescribed to younger, healthier individuals with lower $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores compared with patients receiving warfarin. Other factors that influence the likelihood that a patient will receive a NOAC include gender (women are 24 percent less likely to receive a NOAC) and income. For every one-point increase in $CHADS_2$ scores, patients were 20 percent less likely to receive a NOAC (OR 0.80; 95 percent CI, 0.76–0.84). Yet clinical trials for these drugs demonstrated the greatest benefit in patients with the highest risk for stroke.[33,34] There is also evidence of greater cost-effectiveness in patients at greater risk for stroke.[46,48]

Cost-Effectiveness of NOACs Versus Warfarin

The higher cost of the NOACs has spurred numerous publications focused upon assessing their cost-effectiveness relative to warfarin. While the drug acquisition cost associated with warfarin is less when compared with NOACs, the majority of analyses determined the new therapies demonstrated cost-effectiveness when all costs — including the additional costs of monitoring associated with warfarin — are considered.[43,46,49-51]

An analysis of medical cost reductions (separate from the cost of the drug) based on the RE-LY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) trials identified an annual cost-savings of $254 (apixaban), $367 (dabigatran), and $88 (rivaroxaban) in patients younger than 75 years of age, and of $825 for apixaban and $23 for rivaroxaban annually in those older than 75.[52] Another analysis of RE-LY, however, determined that warfarin was more cost-effective in patients with a moderate risk of stroke (assuming good control of INR) compared with dabigatran, which was more cost-effective in a higher-risk population.[46] A recent European study reached the same conclusion.[48] A 2014 study comparing the price of treatments for NVAF reported cost-savings associated with the NOACs to be slightly greater, with savings of $204 (dabigatran 150 mg), $140 (rivaroxaban), $495 (apixaban), and $340 (edoxaban). Details are noted in Table 2.[47]

A review of 17 publications evaluating the cost-effectiveness of dabigatran, rivaroxaban, and apixaban highlighted the heterogeneity of the studies. Researchers in the various studies used different methods of calculating incremental cost-effectiveness ratios, and assumptions and clinical parameters varied as well. The studies assessed did not evaluate cost-effectiveness in actual clinical practice. Nonetheless, the authors of the review concluded that, overall, the studies demonstrated significant cost benefits for NOACs relative to warfarin or aspirin, stating that the research regarding the new therapies suggested that "the clinical benefits of each … justifies their respective costs."[50]

Implications for Managed Care

Determining the appropriate placement of the NOACs on plan formularies requires an evaluation of the pros and cons of each of these agents relative to each other and to warfarin. A thorough assessment of the value of these therapies must consider the financial and clinical benefits as well as the impact on patients. This may include the potential for increased adherence, lack of required therapeutic monitoring, and the possibility of reducing costs related to stroke and bleeding.[53] The NOACs may offer the potential to improve clinical and economic outcomes as well as patient quality of life, should they be thoroughly considered and successfully adopted into health plan formularies and physician prescribing habits.

Table 2 Differences in Medical Costs Among NVAF Patients Treated with NOACs vs. Warfarin[47]

Outcomes	Dabigatran - 150 mg vs. warfarin ($/patient-yr)	Rivaroxaban vs. warfarin ($/patient-yr)	Apixaban vs. warfarin ($/patient-yr)	Edoxaban - 60 mg vs. warfarin ($/patient-yr)
Primary Efficacy Endpoints				
Ischemic or uncertain type of stroke	-$126	-$40	-$37	$0
Hemorrhagic stroke	-$161	-$104	-$132	-$124
Systemic embolism	-$9	-$32	-$3	-$9
Secondary Efficacy Endpoints				
Myocardial infarction	$71	-$88	-$30	-$19
Pulmonary embolism or deep-vein thrombosis	$11	-$1	-$2	$1
Safety Endpoints				
Major bleedings — excluding hemorrhagic stroke	$12	$122	-$280	-$181
Clinically relevant non-major bleedings	$0	$2	-$5	-$8
Other minor bleedings	-$1	$0	-$6	-$1
Total Medical Cost Difference	**-$204**	**-$140**	**-$495**	**-$340**

References

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):e199-e267. **http://circ.ahajournals.org/content/130/23/e199.**
2. Reiffel JA. New versus traditional approaches to oral anticoagulation in patients with atrial fibrillation. *Am J Med*. 2014;127(4):e15. **www.amjmed.com/article/S0002-9343(13)00441-5/pdf.** Accessed April 23, 2015.
3. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology*. 2003;22(2):118-123.
4. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: A report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.
5. Singh SN. Costs and clinical consequences of suboptimal atrial fibrillation management. *Clinicoecon Outcomes Res*. 2012;4:79-90.
6. Santangeli P, Di Biase L, Bai R, et al. Atrial fibrillation and the risk of incident dementia: A meta-analysis. *Heart Rhythm*. 2012;9(11):1761-1768.
7. Patel AA, Ogden K, Veerman M, et al. The economic burden to Medicare of stroke events in atrial fibrillation populations with and without thromboprophylaxis. *Popul Health Manag*. 2014;17(3):159-165.
8. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: Implications for healthcare planning. *Circulation*. 2014;129(23):2371-2379.
9. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112(8):1142-1147.
10. Boccuzzi SJ, Martin J, Stephenson J, et al. Retrospective study of total healthcare costs associated with chronic nonvalvular atrial fibrillation and the occurrence of a first transient ischemic attack, stroke or major bleed. *Curr Med Res Opin*. 2009;25(12):2853-2864.
11. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14(10):1385-1413.
12. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-2104.
13. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2014;30(10):1114-1130.
14. Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med*. 1999;131(7):492-501.
15. Fernandez MM, von Scheele B, Hogue S, et al. Review of challenges in optimizing oral anticoagulation therapy for stroke prevention in atrial fibrillation. *Am J Cardiovasc Drugs*. 2013;13(2):87-102.
16. Nelson WW, Wang L, Baser O, et al. Out-of-range international normalized ratio values and healthcare cost among new warfarin patients with non-valvular atrial fibrillation. *J Med Econ*. 2015;18(5):333-340.
17. Reynolds MR, Shah J, Essebag V, et al. Patterns and predictors of warfarin use in patients with new-onset atrial fibrillation from the FRACTAL Registry. *Am J Cardiol*. 2006;97(4):538-543.
18. Parker CS, Chen Z, Price M, et al. Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: Results from the IN-RANGE study. *J Gen Intern Med*. 2007;22(9):1254-1259.
19. Casciano JP, Dotiwala ZJ, Martin BC, et al. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: A commercial insurer perspective. *J Manag Care Pharm*. 2013;19(4):302-316.
20. Tsai K, Erickson SC, Yang J, et al. Adherence, persistence, and switching patterns of dabigatran etexilate. *Am J Manag Care*. 2013;19(9):e325-e332. **www.ajmc.com/journals/issue/2013/2013-1-vol19-n9/Adherence-Persistence-and-Switching-Patterns-of-Dabigatran-Etexilate.**
21. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: Insights from the Veterans Health Administration. *Am Heart J*. 2014;167(6):810-817.
22. Ten Cate H. New oral anticoagulants: Discussion on monitoring and adherence should start now! *Thromb J*. 2013;11(1):8.
23. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):7S-47S. **http://journal.publications.chestnet.org/article.aspx?articleid=1159399.**
24. Kirley K, Qato DM, Kornfield R, et al. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):615-621.
25. Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131(12):927-934.
26. Bravata DM, Rosenbeck K, Kancir S, et al. The use of warfarin in veterans with atrial fibrillation. *BMC Cardiovasc Disord*. 2004;4(1):18.
27. Yu HC, Tsai YF, Chen MC, et al. Underuse of antithrombotic therapy caused high incidence of ischemic stroke in patients with atrial fibrillation. *Int J Stroke*. 2012;7(2):112-117.
28. Ogilvie IM, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: A systematic review. *Am J Med*. 2010;123(7):638-645 e634.
29. Man-Son-Hing M, Laupacis A. Anticoagulant-related bleeding in older persons with atrial fibrillation: Physicians' fears often unfounded. *Arch Intern Med*. 2003;163(13):1580-1586.
30. Robert-Ebadi H, Righini M. Anticoagulation in the elderly. *Pharmaceuticals (Basel)*. 2010;3:3543-3569.
31. Caro JJ. An economic model of stroke in atrial fibrillation: The cost of suboptimal oral anticoagulation. *Am J Manag Care*. 2004;10(14 Suppl):S451-S458; discussion S458-S461.
32. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
33. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.
34. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.
35. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
36. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *The Lancet*. 2014;383(9921):955-962.
37. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: Opportunities and challenges. *Arterioscler Thromb Vasc Biol*. 2015;35(5):1056-1065.
38. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214.
39. Boehringer Ingelheim submits applications for approval of idarucizumab, specific reversal agent to dabigatran etexilate (Pradaxa®), to EMA, FDA and Health Canada. Boehringer Ingelheim. News release. March 3, 2015. **www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/03_march_2015_dabigatranetexilate.html.** Accessed April 22, 2015.
40. Peck P. Pradaxa, Xarelto, Eliquis: NOACs' reversal a key? MedPage Today website. **www.medpagetoday.com/Cardiology/Prevention/45371.** April 22, 2014. Accessed March 30, 2015.
41. Weitz JI. Anticoagulation therapy in 2015: Where we are and where we are going. *J Thromb Thrombolysis*. 2015;39(3):264-272.
42. Steinberg BA, Holmes DN, Piccini JP, et al. Early adoption of dabigatran and its dosing in U.S. patients with atrial fibrillation: Results from the outcomes registry for better informed treatment of atrial fibrillation. *J Am Heart Assoc*. 2013;2(6):e000535.
43. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation—quality and cost implications. *Am J Med*. 2014;127(11):1075-1082 e1071.
44. Helfand C. Daiichi's Savaysa goes up against next-gen anticoagulant trio in heated market race. FiercePharma website. **www.fiercepharma.com/story/daiichis-savaysa-goes-against-next-gen-anticoagulant-trio-heated-market-rac/2015-01-09.** January 9, 2015. Accessed April 2, 2015.
45. Savaysa [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2015.
46. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123(22):2562-2570.
47. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Comparison of medical costs avoided among nonvalvular atrial fibrillation patients treated with dabigatran, rivaroxaban, apixaban, and edoxaban vs. warfarin. American College of Cardiology 64th Annual Scientific Sessions. San Diego, CA. March 14-16, 2015.
48. Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. *Pharmacoeconomics*. 2015;33(4):395-408.
49. Harrington AR, Armstrong EP, Nolan PE, Jr., et al. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke*. 2013;44(6):1676-1681.
50. Kansal AR, Zheng Y, Pokora T, et al. Cost-effectiveness of new oral anticoagulants in the prevention of stroke in patients with atrial fibrillation. *Best Pract Res Clin Haematol*. 2013;26(2):225-237.
51. Lee S, Anglade MW, Pham D, et al. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. *Am J Cardiol*. 2012;110(6):845-851.
52. Deitelzweig S, Amin A, Jing Y, et al. Medical cost reductions associated with the usage of novel oral anticoagulants vs warfarin among atrial fibrillation patients, based on the RE-LY, ROCKET-AF, and ARISTOTLE trials. *J Med Econ*. 2012;15(4):776-785.
53. Biskupiak J, Ghate SR, Jiao T, et al. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. *J Manag Care Pharm*. 2013;19(9):789-798.

The Business Role of Compliance in Medicare Part D

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You might roll your eyes when you think about the role of compliance within your organization, concerned that once compliance is involved, the deal you have been negotiating will be stalled. However, I can assure you that most compliance professionals do not wake up each morning and think, "I wonder how I can hinder business today?" Rather, we often lie awake at night pondering what law, regulation, or guidance that we are missing that is going to get our company into trouble.

In the world of Medicare Part D, those concerns are amplified, and for good reason. Medicare Part D, the federal program that governs voluntary prescription drug benefits to Medicare-eligible beneficiaries, is one of the most highly regulated federal programs. The Centers for Medicare & Medicaid Services (CMS), the agency that oversees the Medicare Part D program, has issued volumes of regulations and guidance documents that Medicare Part D Plans ("Plans") and their subcontractors, called "first tier, downstream and related entities," or "FDRs," must follow. These documents include rules as substantive as outlining how Plans must respond to beneficiary appeals and grievances, and as administrative as specifying the font size required for certain marketing materials. CMS releases these requirements and guidelines in federal regulations, in government manuals, and also in letter correspondence, which it releases through the Health Plan Management System, or HPMS.

Plans must implement specific Part D compliance programs within their organizations.[1] The elements of a Part D compliance program stem from Congress's vision for a program to control fraud, abuse, and waste within Part D,[1] and are based on the seven elements of an effective compliance program found in the Federal Sentencing Guidelines, including:

a) Written policies, procedures, and standards of conduct
b) The designation of a compliance officer and a compliance committee who report directly to the Plan's chief executive or other senior management
c) Effective training and education for employees, including the chief executive and senior managers, governing body members, and FDRs

d) Effective lines of communication between the compliance officer, members of the compliance committee, the Plan's employees, managers and governing body, and FDRs
e) Well-publicized disciplinary standards through the implementation of procedures which encourage good faith participation in the compliance program
f) An effective system for routine monitoring and identification of internal and external compliance risks
g) Procedures for promptly responding to compliance issues as they are raised, investigating potential compliance problems as identified, correcting such problems promptly and thoroughly, and ensuring ongoing compliance with CMS requirements[2]

CMS typically makes annual changes to existing regulations that Plans must implement within their organizations. CMS also releases hundreds of guidance documents through HPMS each year that Plans must monitor and incorporate into their business processes. The potential to miss something buried in one of these memos is real, and the penalties for failing to comply with these requirements, as discussed later, can be severe. For this reason, it is imperative that compliance departments and the appropriate business teams work together to review and understand guidance issued by CMS to ensure that the company implements any necessary changes.

With this backdrop, there are several reasons why Plans and FDRs must treat compliance as an important part of the business of providing Part D products and services:

1. Effective compliance programs are designed to protect benefits and beneficiaries.
First and foremost, an effective compliance program is designed to protect Medicare benefits and beneficiaries. Plans receive federal subsidies to provide prescription drug benefits, and CMS expects that such benefits are administered to and for the benefit of Medicare beneficiaries.

CMS states in its enforcement letters that a "Medicare Prescription Drug Plan sponsor's central mission is to provide Medicare enrollees with prescription drug benefits within a framework of Medicare requirements that provide enrollees with a number of protections." Penalties are levied against those Plans whose failures in certain areas result in enrollees not receiving their benefits in the form or manner in which they are entitled under CMS rules.

Moreover, establishing an effective compliance program makes good business sense. Plans with strong compliance programs can improve Part D services by reducing the likelihood of noncompliant behavior and minimizing potential consequences when noncompliance or potential fraud occurs.

2. Effective compliance programs mitigate fraud, waste, and abuse.
Federal regulations require that effective compliance programs include measures that prevent, detect, and correct noncompliance with CMS's program requirements, as well as measures that prevent, detect, and correct fraud, waste, and abuse.[2] A Plan's compliance program must include written policies, procedures, and standards of conduct that articulate the Plan's commitment to comply with all applicable federal and state standards and also discourage behaviors that lead to fraud, waste, and abuse.

Fraud, waste, and abuse represent significant threats to Medicare Part D. The FBI estimates that 3 to 10 percent of all health care billings are lost to fraud each

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year.[3] In 2013, Medicare expenditures totaled approximately $585.7 billion.[4] If the FBI percentages are applied to this amount, the cost of Medicare fraud for the 2013 fiscal year was anywhere from $17.5 billion to $58.5 billion. More on point, the federal government spent about $62 billion on Medicare Part D in 2010,[5] the most recent year with available data. Applying the FBI percentages, this means that between $1.86 billion and $6.2 billion is attributable to fraud in Medicare Part D alone. Further, CMS estimates that the federal government distributed about $65 billion in improper payments (payments that should not have been made or were for an incorrect amount) through Medicare and Medicaid combined in fiscal year 2013.[6] Improper payments occur when benefits are provided in a manner that is noncompliant with Part D program requirements.

CMS distinguishes fraud from waste from abuse. Generally speaking:

• ***Fraud*** means to knowingly and willfully execute, or attempt to execute, a plan to defraud any health care benefit program or to improperly obtain money or property from any health care benefit program.

• ***Waste*** means the overutilization of services or other practices that result in unnecessary costs to the Medicare program.

• ***Abuse*** involves payment for items or services when there is no legal entitlement to that payment, but unlike fraud, the person or entity that received the payment has not knowingly and/or intentionally misrepresented facts to obtain payment.

CMS notes that "abuse cannot be differentiated categorically from fraud because the distinction between 'fraud' and 'abuse' depends on specific facts and circumstances, intent and prior knowledge, and available evidence, among other factors."[7]

Plans receive federal subsidies to provide prescription drug benefits; therefore, they are charged with ensuring these funds are used consistent with Part D regulations and guidance. Plans that fail to identify and prevent activities that do not comply with federal regulations, or that indicate potential fraud, waste, and abuse, can result in improper payments in the Part D program. Effective compliance programs can help to mitigate risks associated with improper payments stemming from such activities.

3. CMS audits compliance programs.

Each year, CMS conducts program audits to evaluate "sponsors' compliance with a number of core program requirements, especially those that safeguard beneficiary access to medically necessary services and prescription drugs."[8] As part of the government's program audits of Part D Plans, CMS audits a Plan's compliance program to determine whether it is effective.

CMS audits all seven elements of the compliance program by pulling five "tracer" samples, and "tracing" each issue as it moves through the compliance program. As the issue is traced through the compliance program, CMS reviews data and documentation related to the respective compliance plan elements (policies and procedures, auditing and monitoring, etc.) and conducts interviews to collect additional information related to the Plan's compliance program. As part of its review, CMS evaluates whether or not Plans "effectively monitor compliance with … Part D program requirements, including compliance with key fraud and abuse program initiatives."[9]

CMS has issued many enforcement actions against Plans whose compliance programs the agency determined were ineffective. Not only can these enforcement actions include severe penalties, they are available for public review and can influence an individual's (or employer group's) decision as to whether or not to enroll in a particular Plan.

4. The penalties can be severe for organizations that are noncompliant.

CMS may levy one or more enforcement actions against Plans that are not compliant with CMS regulations and guidance.[10]

CMS may impose one or more intermediate sanctions against Plans that (i) fail to provide medically necessary items and services required under the law or the contract, (ii) impose excess premiums, (iii) expel or refuse to re-enroll a beneficiary, (iv) misrepresent or falsify information furnished to CMS, (v) employ or contract with an excluded individual or entity, (vi) enroll or transfer an individual to a plan without his or her consent, or (vii) fail to comply with marketing restrictions.[11] Intermediate sanctions can include suspension of enrollment, suspension of payment, and/or suspension of marketing to Medicare beneficiaries.[12]

In addition, CMS and the Department of Health and Human Services Office of Inspector General (OIG) can impose a civil monetary penalty (CMP) against Plans for

certain violations.[12] CMS can impose up to $25,000 per enrollee for each identified deficiency, and can impose an additional $10,000 penalty for each week the deficiency remains uncorrected.[13] In determining the appropriate CMP, CMS will consider the nature of the conduct, the Part D sponsor's degree of culpability, the harm that resulted or could have resulted, the Plan's financial condition, any prior offenses, and "other matters as justice may require."[13]

Further, CMS may decline to renew a Plan's Part D contract, or in egregious circumstances, may terminate the contract.[14] Such circumstances could include:

- Failure to carry out the contract or do so in a manner inconsistent with efficient and effective administration
- Failure to comply with requirements regarding grievances and appeals, access, marketing, service access, plan and program coordination, and information dissemination
- Failure to provide CMS with valid or accurate risk adjustment, reinsurance, and risk corridor related data or MLR data as required
- Substantial failure to comply with cost and utilization management, quality improvement, medication therapy management and fraud, abuse, and waste program requirements
- Failure to meet CMS performance requirements
- Achievement of fewer than three stars for three consecutive contract years[14]

In 2014, CMS took 35 enforcement actions against insurers that provide Medicare Part C and D coverage,[15] the most it has imposed since 2010.[16] These enforcement actions are all posted on CMS's website. They are embarrassing for Plans, and they can be costly.

CMS expects compliance issues to occur, especially in the context of this incredibly complex federal program. An effective compliance program, however, is designed to limit the occurrence of such issues, identify issues sooner rather than later, and provide a framework for addressing issues that arise.

References

1. Social Security Act. Beneficiary protections for qualified prescription drug coverage. 42 U.S.C. §1860D-4(c)(1)(d). 2005.
2. Voluntary Medicare Prescription Drug Benefit. General provisions: Conditions necessary to contract as a Part D plan sponsor. 42, C.F.R. § 423.504(b)(4)(vi). 2005.
3. Medicare fraud strike force charges 107 individuals for approximately $452 million in false billing. Federal Bureau of Investigation. News release. May 2, 2012. **www.fbi.gov/neworleans/press-releases/2012/medicare-fraud-strike-force-charges-107-individuals-for-approximately-452-million-in-false-billing.** Accessed June 3, 2015.
4. National health expenditure data, NHE fact sheet. Centers for Medicare & Medicaid Services website. **www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet.html.** Accessed June 3, 2015.
5. Spending patterns for prescription drugs under Medicare Part D. Congressional Budget Office website. **www.cbo.gov/sites/default/files/12-01-MedicarePartD.pdf.** December 2011. Accessed June 3, 2015.
6. FY 2013 agency financial report. Department of Health and Human Services website. **www.hhs.gov/afr/2013-hhs-agency-financial-report.pdf.** Accessed June 3, 2015.
7. Medicare prescription drug benefit manual. Centers for Medicare & Medicaid Services. Pub 100-18, Chapter 9, § 20.
8. CMS memorandum, 2015 program audit protocols and process updates. Centers for Medicare & Medicaid Services website. **www.cms.gov/Medicare/Compliance-and-Audits/Part-C-and-Part-D-Compliance-and-Audits/ProgramAudits.html.** February 12, 2015. Accessed June 3, 2015.
9. The 2013 part C and part D program annual audit and enforcement report. Centers for Medicare & Medicaid Services website. **www.cms.gov/Medicare/Compliance-and-Audits/Part-C-and-Part-D-Compliance-and-Audits/Downloads/2013CandDProgramAuditAnnualReport.pdf.** October 16, 2014. Accessed June 3, 2015.
10. Voluntary Medicare Prescription Drug Benefit. Basis for imposing intermediate sanctions and civil money penalties. Other applicable provisions. 42, C.F.R. §§ 423.752 to 423.764. 2005.
11. Voluntary Medicare Prescription Drug Benefit. Basis for imposing intermediate sanctions and civil money penalties.42, C.F.R. § 423.752(a). 2005.
12. Voluntary Medicare Prescription Drug Benefit. Types of intermediate sanctions and civil money penalties. 42, C.F.R. § 423.750(a)(b). 2005.
13. Voluntary Medicare Prescription Drug Benefit. Determinations regarding the amount of civil money penalties and assessment imposed by CMS. 42, C.F.R. § 423.760(a)(b). 2005.
14. Voluntary Medicare Prescription Drug Benefit. Termination of contract by CMS. 42, C.F.R. § 423.509(a). 2005.
15. Part C and D enforcement actions. Centers for Medicare & Medicaid Services website. **www.cms.gov/Medicare/Compliance-and-Audits/Part-C-and-Part-D-Compliance-and-Audits/PartCandPartDEnforcementActions-.html.** Accessed June 3, 2015.
16. Herman B. Medicare is doing more to police Advantage and Part D lapses, but does it matter? Modern Healthcare website. **www.modernhealthcare.com/article/20141204/NEWS/312049934.** December 4, 2014. Accessed June 3, 2015.

Orphan Drugs and the Potential Economic Impact

According to the National Organization for Rare Disorders (NORD), more than 30 million Americans are afflicted with approximately 7,000 rare diseases. Due to the low incidence of these rare diseases, there was little incentive for pharmaceutical manufacturers to develop novel products to treat these patients prior to the 1980s. In an attempt to adjust for the lack of financial incentives, the U.S. government put into place the Orphan Drug Act of 1983. The Orphan Drug Act provides manufacturers with the following incentives:

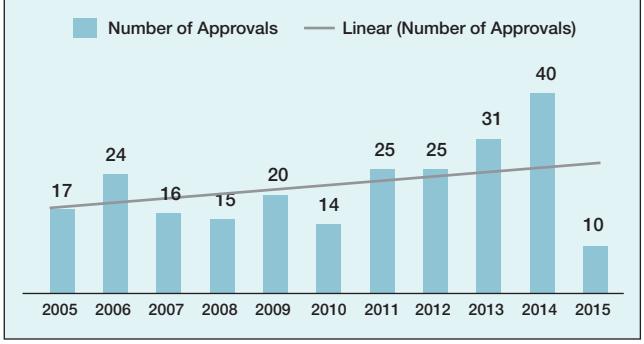
- **Funding** — Federal funding of grants and contracts to perform clinical trials of orphan products awarded annually
- **Credit** — A tax credit of 50 percent for expenditures incurred during the clinical testing phase of orphan drugs being evaluated for their therapeutic potential
- **Exclusivity** — An exclusive right to market the orphan drug for seven years from the date of marketing approval[1]

The approval of the Orphan Drug Act created a substantial market opportunity for pharmaceutical companies and has resulted in a dramatic increase in new drug approvals that address rare diseases. Unfortunately, the innovation in orphan drug development often comes at a premium price. In 2014, there were 41 new drug approvals, 17 (41 percent) of which were orphan drugs. The average annual cost of orphan therapies is $137,782, compared with $20,875 for a nonorphan drug.[2,3] Since 2010, there has been an average of 27 orphan drug approvals per year. Despite their limited utilization, spending on orphan drugs is estimated to comprise approximately 6 percent of total pharmaceutical sales, an increase from less than 1 percent in 2001. It is predicted that orphan drugs will account for 19 percent of total prescription drug sales by 2020.[4]

As a result of this influx of orphan drug approvals, health plans have been evaluating opportunities to ensure appropriate management of these products from both a clinical and financial perspective. Unfortunately, due to the high cost associated with many of these therapies, it may only take one or two patients to generate a financial concern, especially within regional health plans. Orphan diseases vary in prevalence and, typically, the lower the incidence of a certain disease, the higher the cost of the treatment option. Orphan drugs used to treat diseases that affect 20 or fewer patients per million (0.2 per 10,000) are known as ultra rare orphan drugs.[3] These drugs are usually associated with the highest cost.

A simple projection of the potential yearly impact of ultra rare orphan drugs for a hypothetical plan of 1 million members is presented in Table 1. Using assumptions identified in Table 1 for average approvals and average pricing of new ultra rare orphan drugs, the estimated annual impact per million lives is $18,600,570, or $1.55 per-member per-month (PMPM). To put some context

Figure 1: Number of Orphan Drug Approvals[2]*



*Orphan drug approvals in 2015 as of March 2015.

around this estimate, it assumes that only half of the indications for new orphan drugs are for ultra rare disorders and that there is only 50 percent market uptake with a newly approved treatment. A sensitivity analysis of 30 percent shows an annual impact range of $13 million to $24 million per million lives, or a range of $1 to $2 PMPM.

This helps to identify the important need for management solutions for orphan diseases, in general. Expertise in the management and understanding of these small subpopulations is important to ensure appropriate patient management. Appropriate coverage and utilization management decisions need to be made for these low-utilization products to protect against financial instability and ensure affordability. Currently, management strategies include the implementation of prior authorization and medical necessity criteria, specialty distribution, step edits, and high patient cost share. Furthermore, an emphasis should be placed on limiting inappropriate waste that can occur with special populations. Though these strategies currently exist, it may be beneficial to develop a solution for small population management, as a whole.

It is important to keep in mind that orphan drugs are not excused from clinical trial and outcomes requirements. Although these products are generally studied in relatively small sample sizes (due to the small prevalence of the conditions), outcomes demonstrated in randomized controlled trials should remain the primary factor when evaluating management options.

Table 2 highlights some of the unique orphan drugs approved by the FDA, a few of which may fly under the radar of health plans. The data in the table are estimates based on available information at the time of publication and are presented as an example of ultra rare orphan drug diseases. Products such as Cinryze® and Kalydeco® have already made the list of health plan top priorities, but it is important to understand the financial impact that may be associated with other products. Pricing and theoretical projections may differ due to weight-based dosing, frequency, duration of therapy, and site of service. For demonstration purposes, general estimations of product cost are included in the table. The orphan drugs included in the table are Soliris® (eculizumab), Elaprase® (idursulfase), Naglazyme® (galsulfase), Cinryze® (C1 esterase inhibitor [human]),

Table 1 **Impact of Ultra Rare Orphan Drug Approvals**

	Assumptions	Plan Population Estimates	
Plan size:	—	1,000,000	
Assumed average prevalence:	0.00002	20 patients per million lives	
Average number of indications since 2010 (assuming half are ultra rare):	13.5	270 eligible ultra rare orphan disease patients per million lives per year	
Market uptake of new therapies:	50%	135 ultra rare orphan disease patients per million lives per year	
Average price of orphan drug:	$137,782	—	
	Estimated Yearly Impact	**Sensitivity Analysis**	
Estimated yearly budget impact of new ultra rare orphan drug approvals per million lives:	$18,600,570	-30%	+30%
		$13,020,399	$24,180,741
PMPM:	$1.55	-30%	+30%
		$1.09	$2.02

Table 2 Select Orphan Drugs and Estimated Financial Impact[5–19]**

Brand Name	Manufacturer	Indication	Prevalence	Annual Cost Per Patient	Number of Patients Per Million Members	Annual Cost Per Million Members
Soliris	Alexion Pharmaceuticals	Paroxysmal nocturnal hemoglobinuria (PNH)	1 per 1,000,000 people	$497,751	1	$497,751
Elaprase	Shire	Hunter syndrome	1 per 100,000 to 1 per 170,000	$375,000	7.5	$2.8 million
Naglazyme	BioMarin	Mucopolysaccharidosis VI (MPS VI)	1 per 215,000 people	$365,000	4	$1.46 million
Cinryze	Shire ViroPharma Inc.	Hereditary angioedema (HAE)	1 per 50,000 people	$375,000	20	$7.5 million
Folotyn	Allos Therapeutics	Relapsed or refractory peripheral T-cell lymphoma	1 per 100,000 people	$120,000	10	$1.2 million
Kalydeco	Vertex Pharmaceuticals	Cystic fibrosis***	150 total patients in the United States	$307,236	1	$307,236
Myozyme	Genzyme Corporation	Pompe disease	1 in 40,000	$300,000	25	$7.5 million

**The data in the table are estimates based on available information at the time of publication and are presented as an example of ultra rare orphan drug diseases.
***Indicated only for these gene mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R[15]

Table 3 Select Orphan Drug Pipeline for 2015[20]

Drug	Indication	Manufacturer	Route	U.S. Population	Estimated Approval
Asfotase alfa	Hypophosphatasia	Alexion Pharmaceuticals	SC	3,000	August 2015
Kanuma	LAL deficiency	Synageva	IV infusion	3,000	September 2015
Uptravi	Pulmonary arterial hypertension (PAH)	Actelion	Oral	40,000	December 2015

Folotyn® (pralatrexate injection), Kalydeco® (ivacaftor), and Myozyme® (alglucosidase alfa).

Soliris was approved by the FDA in March 2007 for the treatment of a rare blood disorder called paroxysmal nocturnal hemoglobinuria (PNH), a condition that affects 4,000 to 6,000 patients in the United States, which translates to an estimated annual incidence rate of one person per million.[5,6]

In July 2006, the FDA approved Elaprase for the treatment of Hunter syndrome (mucopolysaccharidosis II, or MPS II), a condition with an estimated incidence rate of one per 100,000 to 170,000 people.[7,8]

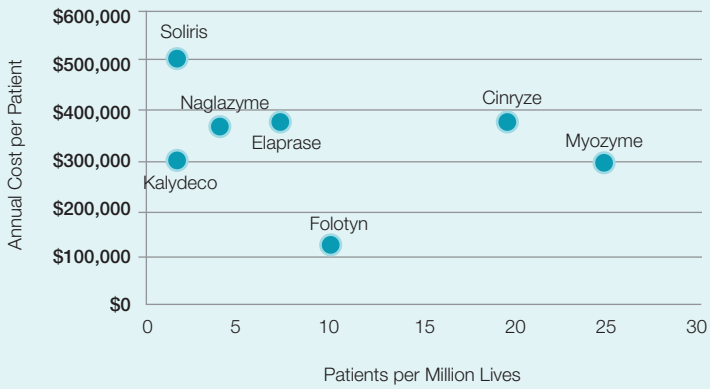
Naglazyme was granted orphan drug approval by the FDA in June 2005 for the treatment of mucopolysaccharidosis VI (MPS VI), which afflicts one person per every 215,000.[9,10]

In October 2008, the FDA granted orphan drug approval for Cinryze in the treatment of patients with hereditary angioedema (HAE), which is characterized as a genetic disorder that causes episodes of edema in the extremities, face, abdomen, and airway passages, and affects one person per every 50,000.[11,12]

Folotyn, approved by the FDA in 2009, was the first treatment approved for relapsed or refractory peripheral T-cell lymphoma, which has an annual incidence rate of one person per every 100,000.[13,14]

Kalydeco was initially approved by the FDA in January 2012 for the treatment of a rare form of cystic fibrosis affecting those who have the specific G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[15,16] In February 2014, Kalydeco received a supplemental FDA approval for an additional eight

Figure 2: Annual Cost per Patient vs. Patients per Million Lives



mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D; approximately 150 people in the United States have one of the above mutations.[15,16] Although Kalydeco has the reputation of being the most expensive oral medication ever approved, it is important to understand the potential impact of new-to-market agents. Vertex has recently received approval for a combination therapy that includes Kalydeco. This combination is indicated for a much larger patient population than the current indication for Kalydeco and has the potential to be a major budget buster in the coming years.

Myozyme was approved by the FDA in April 2006 for the treatment of Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II, which affects one person per every 40,000.[17,18]

On the horizon in 2015, we could see the following impactful drug approvals (see Table 3): asfotase alfa for the treatment of hypophosphatasia, Kanuma™ (sebelipase alfa) for LAL deficiency, and Uptravi® (selexipag) for the treatment of pulmonary arterial hypertension (PAH).[20]

Despite being used in small populations, it is clear that orphan drugs will continue to impact managed care. Many of these therapies are groundbreaking and provide therapeutic opportunities for patients with limited options. Pricing of orphan drug agents is based on a number of factors, including rarity, safety and effectiveness, manufacturing complexity, and potential future indications. From a managed care perspective, it is important to understand the pipeline of rare diseases, ensure appropriate patient management, and develop a strategy for appropriate utilization that incorporates clinical, safety, and economic considerations as more orphan drugs emerge.

References

1. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. *Orphanet J Rare Dis.* 2008, 3:33. **www.ojrd.com/content/3/1/33.**
2. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Novel new drugs 2014 summary. **www.fda.gov/downloads/drugs/developmentapprovalprocess/druginnovation/ucm430299.pdf.** January 2015.
3. EvaluatePharma. Orphan Drug Report 2014. **http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf.** 2014. Accessed April 2015.
4. Helfand C. Report: Orphan drugs to nab 19% of drug sales by 2020—if payers don't balk, that is. FiercePharma website. **www.fiercepharma.com/story/report-orphan-drugs-nab-19-drug-sales-2020-if-payers-dont-balk/2014-11-03.** November 2014. Accessed April 2015.
5. Soliris (eculizumab) [product monograph]. Cheshire, CT: Alexion Pharmaceuticals Inc.; April 2014.
6. Paroxysmal nocturnal hemoglobinuria. Mayo Medical Laboratories website. **http://www.mayomedicallaboratories.com/articles/hottopics/2010-12b-pnh.html.** Accessed January 19, 2015.
7. Elaprase (idursulfase) [product monograph]. Lexington, MA: Shire Human Genetic Therapies, Inc.; 2014.
8. Patel P, Suzuki Y, Maeda M, et al. Growth charts for patients with Hunter syndrome. *Mol Genet Metab Rep.* 2014;1:5-18. **www.sciencedirect.com/science/article/pii/S2214426913000037.**
9. Naglazyme (galsulfase) [product monograph]. Novato, CA: BioMarin Pharmaceutical Inc.; 2014.
10. MPS VI (Maroteaux-Lamy syndrome). National MPS Society website. **http://mpssociety.org/mps/mps-vi/.** Accessed January 20, 2015.
11. Cinryze (C1 esterase inhibitor [human]) [product monograph]. Lexington, MA: Shire ViroPharma Inc.; 2014.
12. National Organization for Rare Disorders (NORD). Physician's guide: Hereditary angioedema (HAE). **http://nordphysicianguides.org/hereditary-angioedema/.** 2010. Accessed January 20, 2015.
13. Folotyn (pralatrexate injection) [product monograph]. Westminster, CO: Allos Therapeutics; May 2012.
14. Bodiford A, Bodge M, Talbott M, Reddy N. Profile of belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma. *Onco Targets Ther.* 2014;7:1971-1977. **www.dovepress.com/profile-of-belinostat-for-the-treatment-of-relapsed-or-refractory-peri-peer-reviewed-article-OT.** Accessed January 20, 2015.
15. Kalydeco (ivacaftor) [product monograph]. Boston, MA: Vertex Pharmaceuticals; December 2014.
16. U.S. Food and Drug Administration approves KALYDECO™ (ivacaftor) for use in eight additional mutations that cause cystic fibrosis. Vertex Pharmaceuticals Incorporated. News release. February 21, 2014. **http://investors.vrtx.com/releasedetail.cfm?releaseid=827435.** Accessed January 20, 2015.
17. Myozyme (alglucosidase alfa) [product monograph]. Cambridge, MA: Genzyme Corporation; 2006.
18. Leslie N, Tinkle BT. Glycogen storage disease type II (Pompe disease). *GeneReviews®*. Updated May 9, 2013. **www.ncbi.nlm.nih.gov/books/NBK1261/.**
19. Red Book Online [database]. Truven Health Analytics.
20. Tharaldson A. Specialty pharmaceuticals in development. Presented at Academy of Managed Care Pharmacy Annual Meeting. April 8, 2015. San Diego, CA.

Impact of Site of Care and Adherence on Tysabri Utilization and Outcomes: Evidence from Two Retrospective Studies

Multiple sclerosis (MS) is a specialty disease state that is known to generate significant financial challenges for managed care organizations and employer groups. These economic concerns are largely derived from the cost of pharmacologic therapy and progressive disability associated with disease relapse — a difficult cost to quantify. The majority of pharmacologic therapy used to treat MS falls under the pharmacy benefit, which allows for accurate assessment of utilization, adherence, and cost. However, certain products, such as Tysabri® (natalizumab) and Lemtrada® (alemtuzumab), are infused products and are typically billed under the medical benefit. For these products, information regarding utilization is less readily available and may be subject to a variety of factors that do not necessarily impact pharmacologic agents covered under the pharmacy benefit (i.e., site of care). To better understand the utilization of Tysabri in real-world patient populations, two retrospective studies were recently conducted.

Site of Care Comparison

The first study analyzed the impact that site of care (SOC) has on utilization, adherence, and cost for Tysabri across four U.S. geographical areas (Northeast, Southeast, Midwest, and West Coast).[1] This study was a retrospective analysis of real-world medical claims data from four regional health plans. All adult patients with a diagnosis of MS who were administered Tysabri between January 1, 2013, and December 31, 2013, were included in the analysis. Differences in utilization and expenditure of Tysabri within various SOCs were evaluated.[1] A total of 582 patients were administered Tysabri, which correlates to 4,347 total claims.[1] This assessment offers insight into the costs and practice patterns with a focus on geographical differences in SOC utilization.

Patterns and costs associated with the administration of Tysabri within three SOCs were assessed:

- Home Infusion/Specialty Pharmacy Provider (HI/SPP)
- Hospital Outpatient Facility (Hospital OP)
- Physician Office or Freestanding Infusion Center (FSIC)

The percentage of claims administered in each SOC were similar across all regions with the exception of a higher proportion of HI/SPP utilization in the Midwest.[1] The utilization associated with the administration of Tysabri within each SOC is outlined in Table 1 for each region.[1] Using the cost of physician office administration as a reference point, the relative allowed amount per claim was calculated for each SOC and region. Regardless of the region, hospital outpatient administration was consistently more costly than physician office administration.

Table 1 Utilization Breakdown by Region and Site of Care (SOC)[1]

	SOC	Percent of Allowed Amount by Region	Number of Claims	Relative Allowed Amount per Claim*
Northeast	Home Infusion/Specialty Pharmacy Provider (HI/SPP)	5.72%	188	0.95
	Hospital Outpatient Facility (Hospital OP)	56.66%	1,073	1.65
	Physician Office or Freestanding Infusion Centers	37.62%	1,176	1
Southeast	HI/SPP	3.23%	42	0.92
	Hospital OP	43.95%	457	1.15
	Physician Office or Freestanding Infusion Centers	52.82%	629	1
Midwest	HI/SPP	20.97%	157	0.95
	Hospital OP	45.35%	226	1.43
	Physician Office or Freestanding Infusion Centers	33.68%	240	1
West Coast	HI/SPP	1.82%	4	0.86
	Hospital OP	48.85%	62	1.49
	Physician Office or Freestanding Infusion Centers	49.33%	93	1

*Relative allowed amount per claim using physician office utilization as comparative index point

Figure 1: Difference Between Percent of Cost and Percent of Claims by Site of Care[1]

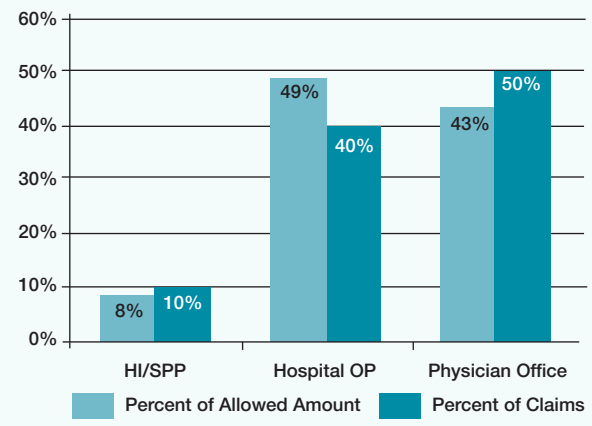


Figure 2: Relative Allowed Amount per Claim by Region and SOC[1]

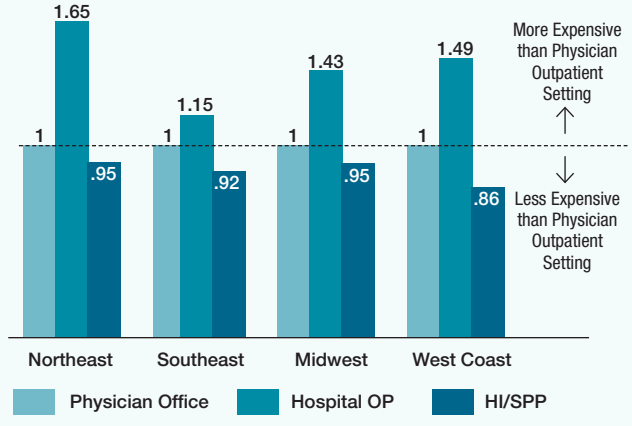


Table 2 Mean Relapse Outcomes in Year Prior to Treatment Transition[2]

	Nonpersistent in Year Post	Persistent in Year Post
Nonpersistent in Year Prior	n = 1,451	n = 132
Annual number of relapses in year prior	0.67* (0.52, 0.81)	0.47 (0.27, 0.67)
Annual relapse cost in year prior ($)	3,816* (3,029, 4,602)	2,062 (855, 3,269)
Persistent in Year Prior	n = 731	n = 2,456
Annual number of relapses in year prior	0.45* (0.37, 0.54)	0.28 (0.24, 0.32)
Annual relapse cost in year prior ($)	2,645* (1,753, 3,537)	1,289 (988, 1,590)

Note: Data are means (95% CI in prior year. Costs in 2012 U.S. dollars.)
*Significant at P <0.05 when compared with reference group persistent in year prior and year post
CI = confidence interval

However, the percent of total spending within each SOC is not directly correlated with the percent of claims. As shown by Figure 1, hospital outpatient utilization is notably different from physician office administration. Although physician office administration represents the highest percentage in terms of total claims (50 percent of total claims), hospital outpatient utilization is associated with the highest cost (49 percent of total cost). This highlights the reimbursement discrepancy that exists between physician office administration and hospital outpatient utilization.

This retrospective analysis demonstrates the impact that SOC can have on costs and potential for introducing additional, possibly unnecessary costs. The analysis demonstrated that SOC utilization differs slightly geographically; however, hospital outpatient utilization overall was associated with a 50 percent increase in cost in relation to physician office administration.

The final step of this analysis considered variations in adherence to Tysabri therapy. Adherence rates in various SOCs were comparable, with the exception of lower adherence in the Southeast in patients treated in the hospital outpatient setting.[1] These patients demonstrated an adherence rate of 82 percent compared with adherence of more than 92 percent for patients receiving Tysabri through alternative SOCs.[1]

Impact of Adherence on Relapse

The assessment of adherence takes on increased relevance when giving consideration to the findings of a recent study published in the *Journal of Managed Care and Specialty Pharmacy*. This retrospective analysis was undertaken to assess relapse activity for MS patients utilizing Tysabri therapy and the impact that adherence had on relapse rates.

The objectives of this analysis were to examine the impact of persistent use of Tysabri on relapse-related outcomes compared with patients transitioning to inconsistent or nonpersistent Tysabri use, and to examine the impact of persistence patterns of Tysabri on relapse-related outcomes.[2] Data was obtained retrospectively using a claims database and identified members who were initiated on Tysabri and had at least two years of follow-up care.[2] Relapse was defined as an MS-related hospitalization or outpatient visit including treatment with intravenous (IV) therapy or oral steroid claims within seven days.[2] The analysis compared changes in Tysabri persistence status and applied this information to differences in average relapse rates and average relapse-related costs.[2]

A total of 2,407 Tysabri patients were followed, resulting in 4,770 year-to-year treatment patterns observed over at least two years.[2] These were identified as patients who:

- Were persistent and remained persistent
- Were nonpersistent but became persistent
- Were persistent but became nonpersistent
- Were originally nonpersistent and remained nonpersistent[2]

Relapses and relapse-related costs were highest for those who were nonpersistent and remained nonpersistent with an annualized relapse rate of 0.67 and a relapse-related cost of $3,816.[2] Those who were persistent and remained persistent had the lowest relapse rate and relapse-related cost of 0.28 and $1,289, respectively.[2] The financial implications of nonpersistence are demonstrated in Table 2. There was a statistically significant 52 percent increase in relapse rates and 58 percent increase in relapse-related costs when patients transitioned from persistent to nonpersistent.[2] Transitioning from nonpersistent to persistent was associated with a 32 percent decrease in relapse rates and a 56 percent decrease in relapse-related costs, but this was not determined to be statistically significant.[2] The analysis concluded that significant increases in relapse rates and relapse-related costs were observed when patients who were persistent on Tysabri transitioned to nonpersistent with treatment.[2] The reverse was true in patients who transitioned from nonpersistence to persistence.

These analyses demonstrate opportunities for managing costs associated with the treatment of MS that may include addressing SOC utilization patterns for Tysabri and programs that enhance adherence. As demonstrated, the SOC has a significant impact on the allowed amount per claim for administration of Tysabri. This information presents payors with a potentially meaningful opportunity to manage the costs associated with treatment of MS by reducing the utilization of cost-inefficient administration settings and by identifying regions with a higher percentage of hospital OP utilization.

While there are not meaningful differences in adherence amongst the various SOCs, programs to improve adherence may offer value. They present payors with the potential to impact the rate of relapse associated with fluctuation in utilization and adherence with Tysabri therapy. The data presented indicates that the persistent use of Tysabri is associated with decreased relapses and reduced relapse-related costs. This is relevant as this study demonstrates, for example, that a statistically significant increase in relapses and costs was demonstrated in patients who were persistent and became nonpersistent. Payors can use this information to target patients who are nonpersistent or at risk of becoming nonpersistent in the use of Tysabri therapy as a means of managing the significant increases in relapse-related costs in the MS population.

References

1. Lord TC, Hassan KM, Lopes M. A retrospective analysis of real-world medical data to evaluate differences in utilization and expenditure of natalizumab within various sites of care. Poster session presented at the meeting of the Academy of Managed Care Pharmacy, San Diego, CA. April 2015.
2. McQueen RB, Livingston T, Vollmer T. Increased relapse activity for multiple sclerosis natalizumab users who become nonpersistent: A retrospective study. *JMCP*. 2015;21(3).

PIPELINE TRENDS

NEW DRUG APPROVALS			
Drug	**Manufacturer**	**Approval Date**	**Indication**
Farydak® (panobinostat)	Novartis	February 23, 2015	Histone deacetylase inhibitor for the combination treatment of multiple myeloma
Avycaz™ (avibactam/ ceftazidime)	Actavis	February 25, 2015	Next-generation, non-beta-lactam beta-lactamase inhibitor and third-generation, antipseudomonal cephalosporin antibiotic combination for the treatment of complicated intra-abdominal infections and complicated urinary tract infections
Toujeo® (insulin glargine [rDNA origin])	Sanofi	February 25, 2015	Once-daily, long-acting basal insulin used to improve glycemic control in adults with type 1 and type 2 diabetes
Liletta® (levonorgestrel)	Medicines360 and Actavis	February 26, 2015	Hormonal intrauterine device for use by women to prevent pregnancy for up to three years
Elepsia XR™ (levetiracetam ER)	Sun Pharma	March 2, 2015	Extended release formulation of the antiepileptic drug levetiracetam designed to reduce pill burden in patients receiving high doses for the treatment of partial-onset seizures
Cresemba® (isavuconazonium)	Astellas Pharma	March 6, 2015	Azole antifungal indicated for the treatment of invasive aspergillosis and invasive mucormycosis
Zarxio™ (filgrastim-sndz)	Sandoz	March 6, 2015	Leukocyte growth factor biosimilar to the reference product Neupogen®, indicated for the treatment of neutropenia associated with chemotherapy
Unituxin™ (dinutuximab)	United Therapeutics Corporation	March 10, 2015	Chimeric monoclonal antibody used for the treatment of pediatric neuroblastoma
Cholbam™ (cholic acid)	Asklepion Pharmaceuticals	March 17, 2015	Bile acid preparation for the treatment of patients with bile acid synthesis disorders due to single enzyme defects, and for patients with peroxisomal disorders (including Zellweger spectrum disorders)
Anthrasil™ (anthrax immune globulin)	Emergent BioSolutions, Inc.	March 24, 2015	Treat patients with inhalational anthrax in combination with appropriate antibacterial drugs
Quadracel® (diphtheria and tetanus toxoids and acellular pertussis absorbed by inactivated poliovirus)	Sanofi	March 27, 2015	Vaccine for active immunization against diphtheria, tetanus, pertussis and poliomyelitis in children 4 to 6 years of age
Jadenu™ (deferasirox)	Novartis	March 30, 2015	Formulation of Exjade®, an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older
ProAir® RespiClick (albuterol sulfate)	Teva	April 1, 2015	Breath-actuated, dry powder, short-acting beta-agonist inhaler for the relief of acute asthma symptoms
Corlanor® (ivabradine)	Amgen	April 15, 2015	Hyperpolarization-activated cyclic nucleotide-gated channel blocker to reduce risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure, on maximally tolerated doses of beta-blocker or contraindication to beta-blocker use
Ixinity® (coagulation factor IX [recombinant])	Emergent BioSolutions Inc.	April 29, 2015	Clotting factor IX therapy for the prevention of bleeding in patients with hemophilia B
Kybella™ (deoxycholic acid)	Kythera Biopharmaceuticals Inc.	April 29, 2015	Cytolytic injectable drug indicated to improve the appearance of fullness associated with submental fat (double chin)
Tuzistra™ XR (chlorpheniramine polistirex and codeine polistirex)	Vernalis PLC and Tris Pharma Inc.	April 30, 2015	Extended-release opiate agonist antitussive and histamine-1 receptor antagonist combination indicated for the relief of cough and symptoms associated with upper respiratory allergies or the common cold
Raplixa™ (fibrin sealant [human])	ProFibrix BV	April 29, 2015	Spray-dried fibrin sealant used to help control bleeding during surgery
Stiolto™ Respimat® (tiotropium/ olodaterol)	Boehringer Ingelheim Pharmaceuticals Inc.	May 21, 2015	Long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) fixed-dose combination for the treatment of chronic obstructive pulmonary disease (COPD)
Viberzi™ (eluxadoline)	Allergan	May 27, 2015	Mu-opioid receptor agonist indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults
Kengreal™ (cangrelor)	The Medicines Company	June 22, 2015	Intravenous $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural thrombotic events
Orkambi™ (lumacaftor/ivacaftor)	Vertex Pharmaceuticals	July 2, 2015	For the treatment of cystic fibrosis (CF) in patients ages 12 years and older who are homozygous for the F508del mutation in the CFTR gene

Disclosures: The information contained in Pipeline Trends is current as of July 2015. Estimated dates are subject to change according to additional indication/approvals, patents, patent litigation, etc. Information available from **www.fda.gov**.

NEW FDA-APPROVED INDICATIONS		
Drug	**Approval Date**	**Indication**
Opdivo® (nivolumab)	March 4, 2015	Expanded approval to treat lung cancer
Saphris® (asenapine)	March 13, 2015	Expanded approval for pediatric patients with bipolar I disorder
Viibryd® (vilazodone)	March 16, 2015	Expanded approval for Viibryd 20 mg once daily as a therapeutic dose
Kalydeco® (ivacaftor)	March 17, 2015	Expanded approval for cystic fibrosis in children ages 2 to 5 years with CFTR gene mutations
Eylea® (afibercept)	March 25, 2015	Expanded approval for diabetic retinopathy in patients with diabetic macular edema
Cyramza™ (ramucirumab)	April 24, 2015	Expanded approval for use with FOLFIRI in second-line treatment of metastatic colorectal cancer
Breo® Ellipta® (fluticasone and vilanterol)	April 30, 2015	Expanded approval for the treatment of asthma
Avelox® (moxifloxacin)	May 8, 2015	Expanded approval for treatment of plague
Xifaxan® (rifaximin)	May 27, 2015	Expanded approval for treatment of IBS-D (irritable bowel syndrome with diarrhea)
Rapamune® (sirolimus)	May 28, 2015	Expanded approval for the treatment of lymphangioleiomyomatosis (LAM), a rare, progressive lung disease
Fycompa™ (perampanel)	June 19, 2015	Expanded approval as adjunctive treatment for primary generalized tonic-clonic seizures

NEW FORMULATIONS AND DOSAGE FORMS		
Drug	**Approval Date**	**Advertised Advantage**
Brilinta® (ticagrelor)	March 26, 2015	Tablet available
Minocin® (minocycline)	April 17, 2015	Available as injection
Invega Trinza™ (paliperidone palmitate)	May 18, 2015	Sustained action injection lasting three months

FIRST-TIME GENERIC DRUG APPROVALS		
Generic Product	**Reference Drug**	**Date of Approval**
Bimatoprost ophthalmic solution 0.03%	Lumigan® ophthalmic solution	February 20, 2015
Miglitol	Glyset® tablet	February 24, 2015
Levoleucovorin calcium	Fusilev® injection	March 9, 2015
Darifenacin hydrobromide extended release	Enablex® tablet	March 13, 2015
Tenofovir disoproxil fumarate	Viread® tablet	March 18, 2015
Molindone hydrochloride	Moban® tablet	March 23, 2015
Tolcapone	Tasmar® tablet	March 26, 2015
Sildenafil citrate	Revatio® injection	April 1, 2015
Triamcinolone acetonide	Kenalog™ topical spray	April 13, 2015
Nebivolol hydrochloride	Bystolic™ tablets	April 16, 2015
Glatiramer acetate	Glatopa™ injection	April 16, 2015
Fluorouracil cream 0.5%	Carac® cream	April 20, 2015
Vardenafil hydrochloride	Staxyn™ orally disintegrating tablets	April 22, 2015
Aripiprazole	Abilify® tablets	April 28, 2015
Alosetron hydrochloride	Lotronex® tablets	May 4, 2015
Linezolid	Zyvox® tablets	May 18, 2015
Risedronate sodium	Atelvia® delayed release tablets	May 18, 2015
Tigecycline	Tygacil® injection	May 27, 2015
Moxifloxacin hydrochloride	Moxeza® ophthalmic solution	May 28, 2015
Estradiol	Vagifem® vaginal tablets	May 29, 2015
Zolpidem tartrate	Intermezzo® sublingual tablets	June 3, 2015
Linezolid oral suspension	Zyvox® for oral suspension	June 3, 2015
Eptifibatide	Integrilin® injection	June 5, 2015
Gemifloxacin mesylate	Factive® tablets	June 15, 2015

A Face of Cure* in HCV

For the treatment of chronic genotype 1 (GT1) hepatitis C virus (HCV) infection—an all-oral, interferon-free regimen with 3 distinct direct-acting antivirals

viekira pak™

ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets

*Cure (virologic cure): sustained virologic response (SVR_{12}); HCV ribonucleic acid (RNA) below the lower limit of quantification (<25 IU/mL) 12 weeks after the end of treatment.

INDICATION[1]

VIEKIRA PAK™, with or without ribavirin (RBV), is indicated for the treatment of adult patients with genotype 1 chronic hepatitis C virus infection, including those with compensated cirrhosis.

Limitation of Use:
VIEKIRA PAK is not recommended for use in patients with decompensated liver disease.

IMPORTANT SAFETY INFORMATION[1]

Risks Associated with RBV Combination Treatment
If VIEKIRA PAK is administered with RBV, the contraindications, warnings and precautions (particularly pregnancy avoidance), and adverse reactions for RBV also apply to this combination regimen. Refer to the RBV prescribing information.

CONTRAINDICATIONS

VIEKIRA PAK is contraindicated:

- in patients with severe hepatic impairment due to risk of potential toxicity.
- with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious and/or life-threatening events; strong inducers of CYP3A or CYP2C8, which may lead to reduced efficacy of VIEKIRA PAK; and strong CYP2C8 inhibitors, which may increase dasabuvir levels and the risk of QT prolongation.
- with the following drugs: alfuzosin HCL; carbamazepine, phenytoin, phenobarbital; gemfibrozil; rifampin; ergotamine, dihydroergotamine, ergonovine, methylergonovine; ethinyl estradiol-containing medicines, such as many oral contraceptives; St. John's wort (*Hypericum perforatum*); lovastatin, simvastatin; pimozide; efavirenz; sildenafil (when dosed as Revatio† for pulmonary arterial hypertension); triazolam and oral midazolam.
- in patients with known hypersensitivity (e.g., toxic epidermal necrolysis or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations

- Elevations of ALT to >5x the ULN occurred in 1% of all subjects in clinical trials and were significantly more frequent in females using ethinyl-estradiol-containing medications. In female patients, discontinue ethinyl estradiol-containing medications prior to starting therapy and use alternative methods of contraception during therapy (e.g., progestin only or non-hormonal contraception). Use caution when co-administering VIEKIRA PAK with estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens.

VIEKIRA PAK +/- ribavirin (RBV) cured* chronic HCV in multiple GT1 patient types, including compensated cirrhotics

VIEKIRA PAK +/- RBV was studied in 6 phase III clinical trials that included >2300 adult patients with chronic GT1 HCV[1]

Across patient populations, pooled by recommended treatment regimen[‡] (n=1084), VIEKIRA PAK +/- RBV delivered consistently high cure* rates ranging from 95%–100%[1,2]

SVR_{12} rates

Overall GT1 Patients Cured[1,2*]

(n=1053/1084)

VIEKIRA PAK ⊕/⊖ RBV

(12 OR 24 WEEKS)

Learn more at viekiraHCP.com

[‡]Recommended regimen=ombitasvir, paritaprevir, ritonavir (25/150/100 mg QD) and dasabuvir (250 mg BID) +/- ribavirin (1000 or 1200 mg determined by body weight; divided BID).[1]

- Perform hepatic lab testing on all patients during the first 4 weeks of treatment and as clinically indicated thereafter. If ALT is elevated above baseline levels, repeat testing and monitor closely. Patients should be instructed to consult their doctor without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces. Consider discontinuing VIEKIRA PAK if ALT levels remain persistently >10x the ULN. Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

- The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK and possible development of resistance, or adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

HCV/HIV-1 Co-infected Patients: Risk of HIV-1 Protease Inhibitor Drug Resistance

- The ritonavir component of VIEKIRA PAK is an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance. To reduce this risk, HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.

ADVERSE REACTIONS

- In subjects receiving VIEKIRA PAK with RBV, the most commonly reported adverse reactions (>10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. In subjects receiving VIEKIRA PAK without RBV, the most commonly reported adverse reactions (≥5% of subjects) were nausea, pruritus, and insomnia.

[†]Revatio® is a trademark of its respective owner and not a trademark of AbbVie Inc. The makers of this brand are not affiliated with and do not endorse AbbVie Inc. or its products.

References: 1. VIEKIRA PAK [package insert]. North Chicago, IL. AbbVie Inc. **2.** Data on file. AbbVie Inc.

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

abbvie

VIEKIRA PAK™

(ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) co-packaged for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

Limitation of Use:

VIEKIRA PAK is not recommended for use in patients with decompensated liver disease *[see Use in Specific Populations]*.

CONTRAINDICATIONS

- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- VIEKIRA PAK is contraindicated in patients with severe hepatic impairment due to risk of potential toxicity *[see Use in Specific Populations]*.
- VIEKIRA PAK is contraindicated with:
  - Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Drugs that are strong inducers of CYP3A and CYP2C8 and may lead to reduced efficacy of VIEKIRA PAK.
  - Drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.

Table 1 lists drugs that are contraindicated with VIEKIRA PAK *[see Drug Interactions]*.

Table 1. Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anti-convulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Anti-hyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.
Anti-mycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydro-ergotamine, ergonovine, methyl-ergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phospho-diesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/ hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

- VIEKIRA PAK is contraindicated in patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations

During clinical trials with VIEKIRA PAK with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects *[see Adverse Reactions]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.

These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA PAK *[see Contraindications]*. Alternative methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.

Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA PAK *[see Adverse Reactions]*.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- Consider discontinuing VIEKIRA PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risks Associated With Ribavirin Combination Treatment

If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of VIEKIRA PAK and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions]*. Consider the potential for drug interactions prior to and during VIEKIRA PAK therapy; review concomitant medications during VIEKIRA PAK therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications and Drug Interactions]*.

Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients

The ritonavir component of VIEKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with VIEKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

ADVERSE REACTIONS

If VIEKIRA PAK is administered with ribavirin (RBV), refer to the prescribing information for ribavirin for a list of ribavirin-associated adverse reactions.

The following adverse reaction is described below and elsewhere in the labeling:

- Increased Risk of ALT Elevations *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety assessment was based on data from six Phase 3 clinical trials in more than 2,000 subjects who received VIEKIRA PAK with or without ribavirin for 12 or 24 weeks.

VIEKIRA PAK with Ribavirin in Placebo-Controlled Trials

The safety of VIEKIRA PAK in combination with ribavirin was assessed in 770 subjects with chronic HCV infection in two placebo-controlled trials (SAPPHIRE-I and -II). Adverse reactions that occurred more often in subjects treated with VIEKIRA PAK in combination with ribavirin compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia (see Table 2). The majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE). The proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

Table 2. Adverse Reactions with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to Placebo for 12 Weeks

	SAPPHIRE-I and -II	
	VIEKIRA PAK + RBV 12 Weeks N = 770 %	Placebo 12 Weeks N = 255 %
Fatigue	34	26
Nausea	22	15
Pruritus*	18	7
Skin reactions§	16	9
Insomnia	14	8
Asthenia	14	7

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.
§Grouped terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria.

VIEKIRA PAK with and without Ribavirin in Regimen-Controlled Trials

VIEKIRA PAK with and without ribavirin was assessed in 401 and 509 subjects with chronic HCV infection, respectively, in three clinical trials (PEARL-II, PEARL-III and PEARL-IV). Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with VIEKIRA PAK in combination with ribavirin (see Table 3). The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for both VIEKIRA PAK in combination with ribavirin and VIEKIRA PAK alone.

Table 3. Adverse Events with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to VIEKIRA PAK for 12 Weeks

	PEARL-II, -III and -IV	
	VIEKIRA PAK + RBV 12 Weeks N = 401 %	VIEKIRA PAK 12 Weeks N = 509 %
Nausea	16	8
Pruritus*	13	7
Insomnia	12	5
Asthenia	9	4

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

VIEKIRA PAK with Ribavirin in Subjects with Compensated Cirrhosis

VIEKIRA PAK with ribavirin was assessed in 380 subjects with compensated cirrhosis who were treated for 12 (n=208) or 24 (n=172) weeks duration (TURQUOISE-II). The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with VIEKIRA PAK for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Skin Reactions

In PEARL-II, -III and -IV, 7% of subjects receiving VIEKIRA PAK alone and 10% of subjects receiving VIEKIRA PAK with ribavirin reported rash-related events. In SAPPHIRE-I and -II 16% of subjects receiving VIEKIRA PAK with ribavirin and 9% of subjects receiving placebo reported skin reactions. In TURQUOISE-II, 18% and 24% of subjects receiving VIEKIRA PAK with ribavirin for 12 or 24 weeks reported skin reactions. The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Laboratory Abnormalities

Serum ALT Elevations

Approximately 1% of subjects treated with VIEKIRA PAK experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. The incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol containing medication *[see Contraindications and Warnings and Precautions]*. The incidence of clinically relevant ALT elevations among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy was 3% (2/59).

ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. The majority of these ALT elevations were assessed as drug-related liver injury. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT *[see Warnings and Precautions]*.

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15% of subjects receiving VIEKIRA PAK with ribavirin compared to 2% in those receiving VIEKIRA PAK alone. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with serum ALT elevations.

Anemia/Decreased Hemoglobin

Across all Phase 3 studies, the mean change from baseline in hemoglobin levels in subjects treated with VIEKIRA PAK in combination with ribavirin was -2.4 g/dL and the mean change in subjects treated with VIEKIRA PAK alone was -0.5 g/dL. Decreases in hemoglobin levels occurred early in treatment (Week 1-2) with further reductions through Week 3. Hemoglobin values remained low during the remainder of treatment and returned towards baseline levels by post-treatment Week 4. Less than 1% of subjects treated with VIEKIRA PAK with ribavirin had hemoglobin levels decrease to less than 8.0 g/dL during treatment. Seven percent of subjects treated with VIEKIRA PAK in combination with ribavirin underwent a ribavirin dose reduction due to a decrease in hemoglobin levels; three subjects received a blood transfusion and five required erythropoietin. One patient discontinued therapy due to anemia. No subjects treated with VIEKIRA PAK alone had a hemoglobin level less than 10 g/dL.

VIEKIRA PAK in HCV/HIV-1 Co-infected Subjects

VIEKIRA PAK with ribavirin was assessed in 63 subjects with HCV/HIV-1 co-infection who were on stable antiretroviral therapy. The most common adverse events occurring in at least 10% of subjects were fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%).

Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) subjects. Fifteen of these subjects were also receiving atazanavir at the time of bilirubin elevation and nine also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases *[see Warnings and Precautions and Adverse Reactions]*. No subject experienced a grade 3 ALT elevation.

Seven subjects (11%) had at least one post-baseline hemoglobin value of less than 10 g/dL, and six of these subjects had a ribavirin dose modification; no subject in this small cohort required a blood transfusion or erythropoietin.

Median declines in CD4+ T-cell counts of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively, and most returned to baseline levels post-treatment. Two subjects had CD4+ T-cell counts decrease to less than 200 cells/mm^3 during treatment without a decrease in CD4%. No subject experienced an AIDS-related opportunistic infection.

VIEKIRA PAK in Selected Liver Transplant Recipients

VIEKIRA PAK with ribavirin was assessed in 34 post-liver transplant subjects with recurrent HCV infection. Adverse events occurring in more than 20% of subjects included fatigue 50%, headache 44%, cough 32%, diarrhea 26%, insomnia 26%, asthenia 24%, nausea 24%, muscle spasms 21% and rash 21%. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten subjects underwent a ribavirin dose modification due to decrease in hemoglobin and 3% (1/34) had an interruption of ribavirin. Five subjects received erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

DRUG INTERACTIONS

See also Contraindications and Warnings and Precautions.

Potential for VIEKIRA PAK to Affect Other Drugs

Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of VIEKIRA PAK with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

Potential for Other Drugs to Affect One or More Components of VIEKIRA PAK

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of VIEKIRA PAK with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes. Co-administration of VIEKIRA PAK with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of VIEKIRA PAK.

Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with VIEKIRA PAK, doses should be re-adjusted after administration of VIEKIRA PAK is completed. Dose adjustment is not required for VIEKIRA PAK.

Table 4 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of VIEKIRA PAK. See *Contraindications* for drugs that are contraindicated with VIEKIRA PAK. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 4. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANTIARRHYTHMICS		
amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with VIEKIRA PAK.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When VIEKIRA PAK is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
voriconazole	↓ voriconazole	Co-administration of VIEKIRA PAK with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone	↑ fluticasone	Concomitant use of VIEKIRA PAK with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.
HIV-ANTIVIRAL AGENTS		
atazanavir/ ritonavir once daily	↑ paritaprevir	When coadministered with VIEKIRA PAK, atazanavir 300 mg (without ritonavir) should only be given in the morning.
darunavir/ ritonavir	↓ darunavir (C_{trough})	Co-administration of VIEKIRA PAK with darunavir/ritonavir is not recommended.
lopinavir/ ritonavir	↑ paritaprevir	Co-administration of VIEKIRA PAK with lopinavir/ritonavir is not recommended.
rilpivirine	↑ rilpivirine	Co-administration of VIEKIRA PAK with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
rosuvastatin	↑ rosuvastatin	When VIEKIRA PAK is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day.
pravastatin	↑ pravastatin	When VIEKIRA PAK is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When initiating therapy with VIEKIRA PAK, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑ tacrolimus	When initiating therapy with VIEKIRA PAK, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol	↑ salmeterol	Concurrent administration of VIEKIRA PAK and salmeterol is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS		
buprenorphine/ naloxone	↑ buprenorphine ↑ norbuprenorphine	No dose adjustment of buprenorphine/ naloxone is required upon co-administration with VIEKIRA PAK. Patients should be closely monitored for sedation and cognitive effects.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) (↑ *= increase of more than 20%,* ↓ *= decrease of more than 20%,* ↔ *= no change or change less than 20%).*

Drugs without Clinically Significant Interactions with VIEKIRA PAK

No dose adjustments are recommended when VIEKIRA PAK is co-administered with the following medications: digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, methadone, progestin only contraceptives, raltegravir, warfarin and zolpidem.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

There is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Adequate and well controlled studies with VIEKIRA PAK have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir, ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, VIEKIRA PAK should be used during pregnancy only if clearly needed.

If VIEKIRA PAK is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir, ritonavir, or dasabuvir. For ombitasvir, the highest dose tested produced exposures approximately 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses tested produced exposures approximately 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures approximately 48-fold (rat) or 12-fold (rabbit) the exposures in humans at the recommended clinical dose.

Nursing Mothers

It is not known whether any of the components of VIEKIRA PAK or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIEKIRA PAK and any potential adverse effects on the breastfed child from VIEKIRA PAK or from the underlying maternal condition.

If VIEKIRA PAK is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

Pediatric Use

Safety and effectiveness of VIEKIRA PAK in pediatric patients less than 18 years of age have not been established.

Geriatric Use

No dosage adjustment of VIEKIRA PAK is warranted in geriatric patients. Of the total number of subjects in clinical studies of VIEKIRA PAK, 8.5% (174/2053) were 65 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 subjects, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is not recommended in HCV-infected patients with moderate hepatic impairment (Child-Pugh B). VIEKIRA PAK is contraindicated in patients with severe (Child-Pugh C) hepatic impairment *[see Contraindications].*

Renal Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild, moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment.

Other HCV Genotypes

The safety and efficacy of VIEKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

OVERDOSAGE

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

PATIENT COUNSELING INFORMATION

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

Inform patients to review the Medication Guide for ribavirin *[see Warnings and Precautions].*

Risk of ALT Elevations

Inform patients to watch for early warning signs of liver inflammation, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces, and to consult their health care professional without delay if such symptoms occur *[see Warnings and Precautions and Adverse Reactions].*

Pregnancy

Advise patients to avoid pregnancy during treatment with VIEKIRA PAK with ribavirin. Inform patients to notify their health care provider immediately in the event of a pregnancy. Inform pregnant patients that there is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals *[see Use in Specific Populations].*

Drug Interactions

Inform patients that VIEKIRA PAK may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications, Warnings and Precautions, and Drug Interactions].*

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with VIEKIRA PAK *[see Contraindications and Warnings and Precautions].*

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C virus infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment should be taken.

Missed Dose

Inform patients that in case a dose of ombitasvir, paritaprevir, ritonavir is missed, the prescribed dose can be taken within 12 hours.

In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours.

If more than 12 hours has passed since ombitasvir, paritaprevir, ritonavir is usually taken or more than 6 hours has passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

Instruct patients not to take more than their prescribed dose of VIEKIRA PAK to make up for a missed dose.

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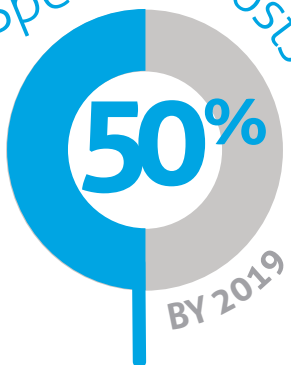

The need for more effective management

Total Specialty Drug Management

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Improve quality and savings through provider network, clinical programs, utilization management and optimizing site of care

FORMULARY & REBATE OPTIMIZATION
Best-in-class specialty formulary and rebates with aggressive contracts for preferred, clinically appropriate, lowest net cost products

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