Spring 2012

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Managed Care Solutions:

- Integrated Approach to Opioid Management
- Improving CMS Quality Performance Measures
- Appropriate Stimulant Management

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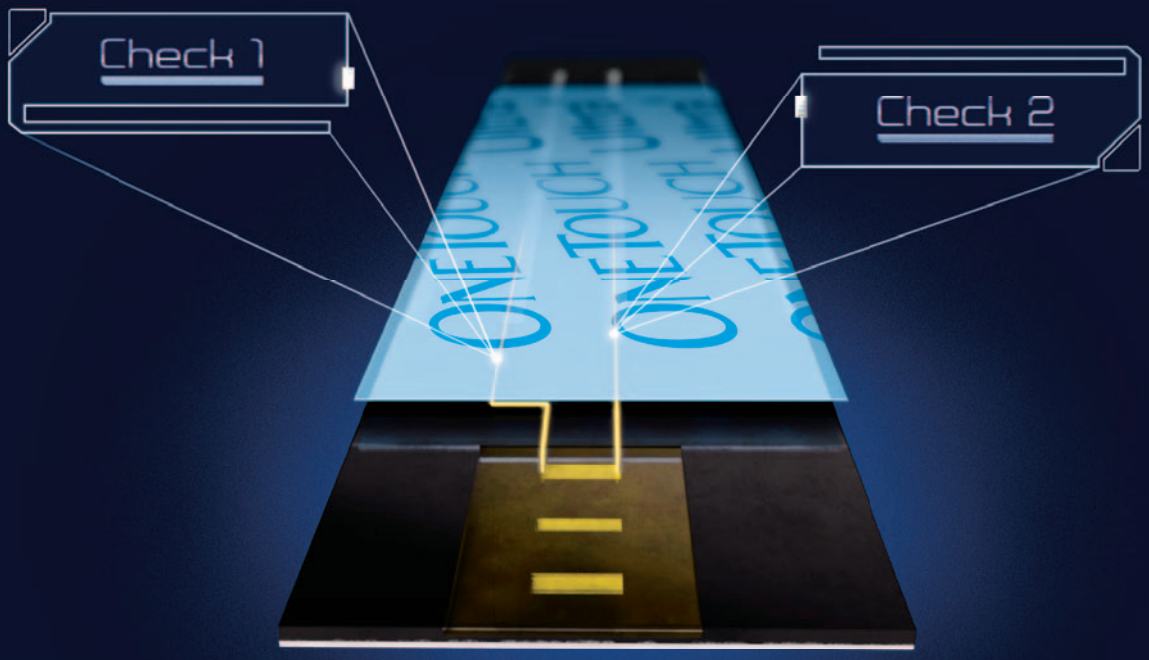

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DoubleSure™ Technology. In every OneTouch® Ultra® Blue Test Strip.

It measures each blood sample not once, but twice, to confirm your result. So you're not just sure about what's happening with your blood sugar—you're DoubleSure.™

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Start

With once-a-day Kombiglyze XR, which delivered strong glycemic control by improving A1C, FPG, and PPG at 24 weeks

For your appropriate adult patients with type 2 diabetes in addition to diet and exercise

ONCE A DAY
kombiglyze™ XR
(saxagliptin and metformin HCl extended-release) tablets

Generally taken once daily with evening meal; gradually titrate dose to reduce GI side effects associated with metformin. Maximum daily recommended dose is 5 mg saxagliptin and 2000 mg metformin XR that can be taken as two 2.5 mg/1000 mg tablets once a day.

Indication and Important Limitations of Use for KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release) tablets

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

KOMBIGLYZE XR has not been studied in patients with a history of pancreatitis.

Important Safety Information for KOMBIGLYZE XR

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately. [See *Warnings and Precautions*]

Contraindications

- Renal impairment (eg, serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- History of a serious hypersensitivity reaction to KOMBIGLYZE XR or saxagliptin (eg, anaphylaxis, angioedema, or exfoliative skin conditions)

Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. After initiating KOMBIGLYZE XR, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue KOMBIGLYZE XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using KOMBIGLYZE XR.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
  —Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR.
  —Metformin: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstituted only after renal function is normal.
- There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in patients with a history of angioedema to another DPP-4 inhibitor as it is unknown whether they will be predisposed to angioedema with KOMBIGLYZE XR.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

Adverse Reactions

- Adverse reactions reported in >5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).
- Adverse reactions reported in ≥5% of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%).
- Adverse reactions reported in ≥5% of treatment-naive patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%).

Drug Interactions

Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.
- **Pediatric Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

Please read adjacent Brief Summary of US Full Prescribing Information for KOMBIGLYZE XR (5/500•5/1000•2.5/1000 mg tablets), including **Boxed WARNING** about lactic acidosis.

Bristol-Myers Squibb

www.kombiglyzexr.com/ad1

AstraZeneca

1612202

KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets **℞ ONLY**

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) should be discontinued and the patient hospitalized immediately. [See *Warnings and Precautions.*]

INDICATIONS AND USAGE

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. [See *Clinical Studies (14)* in Full Prescribing Information.]

Important Limitations of Use

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

KOMBIGLYZE XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using KOMBIGLYZE XR. [See *Warnings and Precautions.*]

CONTRAINDICATIONS

KOMBIGLYZE XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to KOMBIGLYZE XR or saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions. [See *Warnings and Precautions* and *Adverse Reactions.*]

WARNINGS AND PRECAUTIONS

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with KOMBIGLYZE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [see *Warnings and Precautions*].

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur [see *Warnings and Precautions*]. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal, but less than 5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. [See *Warnings and Precautions.*]

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery [see *Contraindications* and *Warnings and Precautions*].

Pancreatitis: There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. After initiation of KOMBIGLYZE XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, KOMBIGLYZE XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using KOMBIGLYZE XR.

Assessment of Renal Function: Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, KOMBIGLYZE XR is contraindicated in patients with renal impairment [see *Contraindications*].

Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and KOMBIGLYZE XR discontinued if evidence of renal impairment is present.

Impaired Hepatic Function: Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, KOMBIGLYZE XR is not recommended in patients with hepatic impairment.

Vitamin B_{12} Concentrations: In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE XR and any apparent abnormalities should be appropriately investigated and managed [see *Adverse Reactions*].

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving KOMBIGLYZE XR.

Surgical Procedures: Use of KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes: A patient with type 2 diabetes previously well controlled on KOMBIGLYZE XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, KOMBIGLYZE XR must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia

Saxagliptin — Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, when used in combination with saxagliptin, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. [See *Adverse Reactions.*]

Metformin hydrochloride — Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

Concomitant Medications Affecting Renal Function or Metformin Disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion [see *Drug Interactions*], should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials: Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on KOMBIGLYZE XR therapy, the drug should be promptly discontinued.

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions.*]

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with KOMBIGLYZE XR.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug.

ADVERSE REACTIONS

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.

Monotherapy and Add-On Combination Therapy

Metformin hydrochloride — In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Saxagliptin — In two placebo-controlled monotherapy trials of 24-week duration, patients were treated with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin immediate-release, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin immediate-release.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin immediate-release trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with saxagliptin 2.5 mg and saxagliptin 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with saxagliptin 2.5 mg or at least 2 patients treated with saxagliptin 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with saxagliptin 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with Saxagliptin 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	Saxagliptin 5 mg N=882	Placebo N=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

*The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with saxagliptin 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with saxagliptin 2.5 mg or saxagliptin 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to saxagliptin is not known.

Adverse Reactions Associated with Saxagliptin Coadministered with Metformin Immediate-Release in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered saxagliptin and metformin in treatment-naive patients.

Table 2: Coadministration of Saxagliptin and Metformin Immediate-Release in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin Immediate-Release (and More Commonly than in Patients Treated with Metformin Immediate-Release Alone)

	Number (%) of Patients	
	Saxagliptin 5 mg + Metformin* N=320	Placebo + Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin immediate-release was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

In patients treated with the combination of saxagliptin and metformin immediate-release, either as saxagliptin add-on to metformin immediate-release therapy or as coadministration in treatment-naive patients, diarrhea was the only gastrointestinal-related event that occurred with an incidence ≥5% in any treatment group in both studies. In the saxagliptin add-on to metformin immediate-release trial, the incidence of diarrhea was 9.9%, 5.8%, and 11.2% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of diarrhea was 6.9% in the saxagliptin 5 mg + metformin immediate-release group and 7.3% in the placebo + metformin immediate-release group.

Hypoglycemia: In the saxagliptin clinical trials, adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively. In the add-on to metformin immediate-release trial, the incidence of reported hypoglycemia was 7.8% with saxagliptin 2.5 mg, 5.8% with saxagliptin 5 mg, and 5.0% with placebo. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of reported hypoglycemia was 3.4% in patients given saxagliptin 5 mg + metformin immediate-release and 4.0% in patients given placebo + metformin immediate-release.

Hypersensitivity Reactions

Saxagliptin — Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. None of these events in patients who received saxagliptin required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Infections

Saxagliptin — In the unblinded, controlled, clinical trial database for saxagliptin to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 saxagliptin-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with saxagliptin use. Causality has not been established and there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. There have been no spontaneous reports of opportunistic infections associated with saxagliptin use.

Vital Signs

Saxagliptin — No clinically meaningful changes in vital signs have been observed in patients treated with saxagliptin alone or in combination with metformin.

Laboratory Tests

Absolute Lymphocyte Counts

Saxagliptin — There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with saxagliptin 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when saxagliptin 5 mg and metformin were coadministered in treatment-naive patients compared to placebo and metformin. There was no difference observed for saxagliptin 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to saxagliptin although some patients had recurrent decreases upon rechallenge that led to discontinuation of saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

Saxagliptin — Saxagliptin did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

Vitamin B_{12} Concentrations

Metformin hydrochloride — Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) and any apparent abnormalities should be appropriately investigated and managed. [See *Warnings and Precautions*.]

Postmarketing Experience: Additional adverse reactions have been identified during postapproval use of saxagliptin. Because these reactions 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.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications* and *Warnings and Precautions*.]
- Acute pancreatitis. [See *Indications and Usage* and *Warnings and Precautions*.]

DRUG INTERACTIONS

Strong Inhibitors of CYP3A4/5 Enzymes

Saxagliptin — Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.]

Cationic Drugs

Metformin hydrochloride — Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in healthy volunteers. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of KOMBIGLYZE XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Use with Other Drugs

Metformin hydrochloride — Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving KOMBIGLYZE XR, the patient should be closely observed for loss of glycemic control. When such drugs are withdrawn from a patient receiving KOMBIGLYZE XR, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B — There are no adequate and well-controlled studies in pregnant women with KOMBIGLYZE XR or its individual components. Because animal reproduction studies are not always predictive of human response, KOMBIGLYZE XR, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (MRHD; saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin — Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the MRHD of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Metformin hydrochloride — Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers: No studies in lactating animals have been conducted with the combined components of KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release). In studies performed with the individual components, both saxagliptin and metformin are secreted in the milk of lactating rats. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

Geriatric Use: *KOMBIGLYZE XR* — Elderly patients are more likely to have decreased renal function. Because metformin is contraindicated in patients with renal impairment, carefully monitor renal function in the elderly and use KOMBIGLYZE XR with caution as age increases. [See *Warnings and Precautions* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.]

Saxagliptin — In the six, double-blind, controlled clinical safety and efficacy trials of saxagliptin, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride — Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney. Because the risk of lactic acidosis with metformin is greater in patients with impaired renal function, KOMBIGLYZE XR should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. [See *Contraindications, Warnings and Precautions,* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.]

OVERDOSAGE

Saxagliptin — In a controlled clinical trial, once-daily, orally-administered saxagliptin in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

Metformin hydrochloride — Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide in Full Prescribing Information.

Instructions

Patients should be informed of the potential risks and benefits of KOMBIGLYZE XR and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

The risks of lactic acidosis due to the metformin component, its symptoms and conditions that predispose to its development, as noted in Warnings and Precautions (5.1), should be explained to patients. Patients should be advised to discontinue KOMBIGLYZE XR immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heart beat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of KOMBIGLYZE XR therapy; however, patients should consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake while receiving KOMBIGLYZE XR.

Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with KOMBIGLYZE XR.

Patients should be informed that acute pancreatitis has been reported during postmarketing use of saxagliptin. Before initiating KOMBIGLYZE XR, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue KOMBIGLYZE XR and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions*].

Patients should be informed that the incidence of hypoglycemia may be increased when KOMBIGLYZE XR is added to an insulin secretagogue (e.g., sulfonylurea).

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during postmarketing use of saxagliptin. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking KOMBIGLYZE XR and seek medical advice promptly.

Patients should be informed that KOMBIGLYZE XR must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Patients should be informed that if they miss a dose of KOMBIGLYZE XR, they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

Healthcare providers should instruct their patients to read the Medication Guide before starting KOMBIGLYZE XR therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

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WELCOME

to this issue

features

trends

What would allow your patients to eat a normal diet?*[1,2]

CREON dosed at 72,000 lipase units **(3 CREON 24,000 capsules)** per meal, and up to 36,000 lipase units per snack, allows your patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy to eat ≥100 g of fat per day

Prescribe your patients 3 CREON 24,000 capsules per meal based on 100 g of fat per day[1]

Capsules shown are not actual size and do not represent exact color shade. Images for illustrative purposes only. *Approximately 100 g of fat per day.

- For all patients, the CREON dose should be individualized and adjusted based on clinical symptoms, the degree of steatorrhea, and the fat content of the diet, and it should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conference Guidelines[1]

INDICATIONS[1]

CREON® (pancrelipase) Delayed Release Capsules is a pancrelipase which is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

IMPORTANT SAFETY INFORMATION

- Fibrosing colonopathy, is associated with high-dose use of pancreatic enzyme replacement in the treatment of cystic fibrosis patients. Exercise caution when doses of CREON exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).
- To avoid irritation of oral mucosa, care should be taken to ensure that CREON is not crushed, chewed or retained in the mouth. CREON should always be taken with food.
- Porcine-derived pancreatic enzyme products contain purines. Caution should be exercised when prescribing CREON to patients with gout, renal impairment, or hyperuricemia.
- There is theoretical risk of viral transmission with all pancreatic enzyme products including CREON.
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.
- Adverse reactions that occurred in at least 2 cystic fibrosis patients (greater than or equal to 4%) receiving CREON were vomiting, dizziness and cough.
- Adverse reactions that occurred in at least 1 chronic pancreatitis or pancreatectomy patient (greater than or equal to 4%) receiving CREON were, hyperglycemia, hypoglycemia, abdominal pain, abnormal feces, flatulence, frequent bowel movements, and nasopharyngitis.
- CREON is not interchangeable with any other pancrelipase product.

CREON® (pancrelipase) Delayed-Release Capsules

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

REFERENCES: 1. CREON [package insert]. North Chicago, IL: Abbott Laboratories. **2.** US Department of Agriculture/Health and Human Services. *Dietary Guidelines for Americans, 2010*. 7th ed. Washington, DC: US Government Printing Office; 2010.

Abbott
A Promise for Life

CREON® (pancrelipase) Delayed-Release Capsules

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

CREON® (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

DOSAGE AND ADMINISTRATION

CREON is not interchangeable with other pancrelipase products.

CREON is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of CREON should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet as described in the Limitations on Dosing below *[see Dosage and Administration and Warnings and Precautions]*.

Administration

Infants (up to 12 months)

CREON should be administered to infants immediately prior to each feeding, using a dosage of 3,000 lipase units per 120 mL of formula or prior to breast-feeding. Contents of the capsule may be administered directly to the mouth or with a small amount of applesauce. Administration should be followed by breast milk or formula. Contents of the capsule should not be mixed directly into formula or breast milk as this may diminish efficacy. Care should be taken to ensure that CREON is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

Children and Adults

CREON should be taken during meals or snacks, with sufficient fluid. CREON capsules and capsule contents should not be crushed or chewed. Capsules should be swallowed whole.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

Dosage

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1, 2, 3] CREON should be administered in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences (also known as Conferences) provided in the following paragraphs, except for infants. Although the Conferences recommend doses of 2,000 to 4,000 lipase units in infants up to 12 months, CREON is available in a 3,000 lipase unit capsule. Therefore, the recommended dose of CREON in infants up to 12 months is 3,000 lipase units per 120 mL of formula or per breast-feeding. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Additional recommendations for pancreatic enzyme therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy are based on a clinical trial conducted in these populations.

Infants (up to 12 months)

CREON is available in the strength of 3,000 USP units of lipase thus infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Do not mix CREON capsule contents directly into formula or breast milk prior to administration *[see Administration]*.

Children Older than 12 Months and Younger than 4 Years

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed CREON dose for an individualized full meal should be given with each snack. The total daily dose should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy

The initial starting dose and increases in the dose per meal should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.

In one clinical trial, patients received CREON at a dose of 72,000 lipase units per meal while consuming at least 100 g of fat per day. Lower starting doses recommended in the literature are consistent with the 500 lipase units/kg of body weight per meal lowest starting dose recommended for adults in the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3, 4] Usually, half of the prescribed CREON dose for an individualized full meal should be given with each snack.

Limitations on Dosing

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3] If symptoms and signs of steatorrhea persist, the dosage may be increased by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age *[see Warnings and Precautions]*. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.[5, 6] Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age.[1] Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs.[1] It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day *[see Dosage and Administration]*.

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth. CREON should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity *[see Dosage and Administration and Patient Counseling Information]*. For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing CREON to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

Potential Viral Exposure from the Product Source

CREON is sourced from pancreatic tissue from swine used for food consumption. Although the risk that CREON will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

Allergic Reactions

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued CREON treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

ADVERSE REACTIONS

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) that are described elsewhere in the label include fibrosing colonopathy, hyperuricemia and allergic 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 the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The short-term safety of CREON was assessed in clinical trials conducted in 121 patients with exocrine pancreatic insufficiency (EPI): 67 patients with EPI due to cystic fibrosis (CF) and 25 patients with EPI due to chronic pancreatitis or pancreatectomy were treated with CREON.

Cystic Fibrosis

Studies 1 and 2 were randomized, double-blind, placebo-controlled, crossover studies of 49 patients, ages 7 to 43 years, with EPI due to CF. Study 1 included 32 patients ages 12 to 43 years and Study 2 included 17 patients ages 7 to 11 years. In these studies, patients were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or matching placebo for 5 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to 6 days. The mean exposure to CREON during these studies was 5 days.

In Study 1, one patient experienced duodenitis and gastritis of moderate severity 16 days after completing treatment with CREON. Transient neutropenia without clinical sequelae was observed as an abnormal laboratory finding in one patient receiving CREON and a macrolide antibiotic.

In Study 2, adverse reactions that occurred in at least 2 patients (greater than or equal to 12%) treated with CREON were vomiting and headache. Vomiting occurred in 2 patients treated with CREON and did not occur in patients treated with placebo; headache occurred in 2 patients treated with CREON and did not occur in patients treated with placebo.

The most common adverse reactions (greater than or equal to 4%) in Studies 1 and 2 were vomiting, dizziness, and cough. Table 1 enumerates adverse reactions that occurred in at least 2 patients (greater than or equal to 4%) treated with CREON at a higher rate than with placebo in Studies 1 and 2.

Table 1: Adverse Reactions Occurring in at Least 2 Patients (greater than or equal to 4%) in Cystic Fibrosis (Studies 1 and 2)

Adverse Reaction	CREON Capsules n = 49 (%)	Placebo n = 47 (%)
Vomiting	3 (6)	1 (2)
Dizziness	2 (4)	1 (2)
Cough	2 (4)	0

An additional open-label, single-arm study assessed the short-term safety and tolerability of CREON in 18 infants and children, ages 4 months to 6 years, with EPI due to cystic fibrosis. Patients received their usual pancreatic enzyme replacement therapy (mean dose of 7,000 lipase units/kg/day for a mean duration of 18.2 days) followed by CREON (mean dose of 7,500 lipase units/kg/day for a mean duration of 12.6 days). There were no serious adverse reactions. Adverse reactions that occurred in patients during treatment with CREON were vomiting, irritability, and decreased appetite, each occurring in 6% of patients.

Chronic Pancreatitis or Pancreatectomy

A randomized, double-blind, placebo-controlled, parallel group study was conducted in 54 adult patients, ages 32 to 75 years, with EPI due to chronic pancreatitis or pancreatectomy. Patients received single-blind placebo treatment during a 5-day run-in period followed by an intervening period of up to 16 days of investigator-directed treatment with no restrictions on pancreatic enzyme replacement therapy. Patients were then randomized to receive CREON or matching placebo for 7 days. The CREON dose was 72,000 lipase units per main meal (3 main meals) and 36,000 lipase units per snack (2 snacks). The mean exposure to CREON during this study was 6.8 days in the 25 patients that received CREON.

The most common adverse reactions reported during the study were related to glycemic control and were reported more commonly during CREON treatment than during placebo treatment.

Table 2 enumerates adverse reactions that occurred in at least 1 patient (greater than or equal to 4%) treated with CREON at a higher rate than with placebo.

Table 2: Adverse Reactions in at Least 1 Patient (greater than or equal to 4%) in the Chronic Pancreatitis or Pancreatectomy Trial

Adverse Reaction	CREON Capsules n = 25 (%)	Placebo n = 29 (%)
Hyperglycemia	2 (8)	2 (7)
Hypoglycemia	1 (4)	1 (3)
Abdominal Pain	1 (4)	1 (3)
Abnormal Feces	1 (4)	0
Flatulence	1 (4)	0
Frequent Bowel Movements	1 (4)	0
Nasopharyngitis	1 (4)	0

Postmarketing Experience

Postmarketing data from this formulation of CREON have been available since 2009. The following adverse reactions have been identified during post approval use of this formulation of CREON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders (including abdominal pain, diarrhea, flatulence, constipation and nausea), skin disorders (including pruritus, urticaria and rash), blurred vision, myalgia, muscle spasm, and asymptomatic elevations of liver enzymes have been reported with this formulation of CREON.

Delayed- and immediate-release pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has been described in the medical literature. The most serious adverse reactions included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus.

DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects

Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CREON should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CREON is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

Pediatric Use

The short-term safety and effectiveness of CREON were assessed in two randomized, double-blind, placebo-controlled, crossover studies of 49 patients with EPI due to cystic fibrosis, 25 of whom were pediatric patients. Study 1 included 8 adolescents between 12 and 17 years of age. Study 2 included 17 children between 7 and 11 years of age. The safety and efficacy in pediatric patients in these studies were similar to adult patients *[see Adverse Reactions]*.

An open-label, single-arm, short-term study of CREON was conducted in 18 infants and children, ages 4 months to six years of age, with EPI due to cystic fibrosis. Patients received their usual pancreatic enzyme replacement therapy (mean dose of 7,000 lipase units/kg/day for a mean duration of 18.2 days) followed by CREON (mean dose of 7,500 lipase units/kg/day for a mean duration of 12.6 days). The mean daily fat intake was 48 grams during treatment with usual pancreatic enzyme replacement therapy and 47 grams during treatment with CREON. When patients were switched from their usual pancreatic enzyme replacement therapy to CREON, they demonstrated similar spot fecal fat testing results; the clinical relevance of spot fecal fat testing has not been demonstrated. Adverse reactions that occurred in patients during treatment with CREON were vomiting, irritability, and decreased appetite *[see Adverse Reactions]*.

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.

Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences *[see Dosage and Administration]*. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy and colonic strictures in children less than 12 years of age *[see Warnings and Precautions]*.

Geriatric Use

Clinical studies of CREON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

There have been no reports of overdose in clinical trials or postmarketing surveillance with this formulation of CREON. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration and Warnings and Precautions]*. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment *[see Warnings and Precautions]*.

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PATIENT COUNSELING INFORMATION

Dosing and Administration

- Instruct patients and caregivers that CREON should only be taken as directed by their healthcare professional. Patients should be advised that the total daily dose should not exceed 10,000 lipase units/kg body weight/day unless clinically indicated. This needs to be especially emphasized for patients eating multiple snacks and meals per day. Patients should be informed that if a dose is missed, the next dose should be taken with the next meal or snack as directed. Doses should not be doubled *[see Dosage and Administration]*.
- Instruct patients and caregivers that CREON should always be taken with food. Patients should be advised that CREON delayed-release capsules and the capsule contents must not be crushed or chewed as doing so could cause early release of enzymes and/or loss of enzymatic activity. Patients should swallow the intact capsules with adequate amounts of liquid at mealtimes. If necessary, the capsule contents can also be sprinkled on soft acidic foods *[see Dosage and Administration]*.

Fibrosing Colonopathy

Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in children below the age of 12 years *[see Dosage and Administration]*.

Allergic Reactions

Advise patients and caregivers to contact their healthcare professional immediately if allergic reactions to CREON develop *[see Warnings and Precautions]*.

Pregnancy and Breast Feeding

- Instruct patients to notify their healthcare professional if they are pregnant or are thinking of becoming pregnant during treatment with CREON *[see Use in Specific Populations]*.
- Instruct patients to notify their healthcare professional if they are breast feeding or are thinking of breast feeding during treatment with CREON *[see Use in Specific Populations]*.

Manufactured by:
Abbott Products GmbH
Hannover, Germany

Marketed By:
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

Ref: 1055216 12E Rev Jul 2011

Revised: July, 2011

853-660203 **MASTER**

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Letter from the President

Susan Petrovas

Dear Managed Care Colleagues,

Susan Petrovas, RPh, President

We value your comments and feedback. Please feel free to contact me directly at **SPetrovas@CDMIhealth.com.**

The concept behind managed care stems from the belief that improved clinical outcomes can be obtained while simultaneously reducing overall healthcare expenditure for both the health plans and their enrolled beneficiaries. Ideally, by improving quality of care and positive clinical outcomes and eliminating waste and inappropriate resource utilization, financial savings should be generated. Using this model of healthcare delivery, one would expect that the majority of business decisions would revolve around an organization's clinical responsibility. As many health plans are under the constant pressure of controlling the escalating healthcare costs, financial implications have become heavily weighted with respect to overall management decisions. With the development of the NCQA HEDIS measures and the CMS Star Ratings, the financially dominated business rationale of the past is finally transitioning to what managed care was designed for: appropriate and responsible clinical management. For those of us lucky enough to have been in the managed care industry for many years, this is a very exciting time.

For many managed care organizations throughout the country, these revised clinical expectations are seen more as a nuisance than a blessing. Developing and implementing comprehensive clinical initiatives and providing the administrative support to ensure appropriate reporting is a daunting task from a resource perspective. However, health plans will now be rewarded for providing their patient populations with industry-leading quality of care. This is a tremendous opportunity for health plans to efficiently manage their total healthcare expenditure while becoming nationally recognized for their clinical management services.

Our clinical team here at CDMI looks forward to being a valuable resource for the management of chronic diseases and quality-improvement initiatives within the managed care industry. Our experienced staff of clinical pharmacists, nurses, and medical data analysts is committed to providing our health plan customers with innovative clinical services designed to address their specific business needs.

As always, thanks for reading!

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

CALL FOR SUBMISSIONS

The goal of *CDMI Report* is to empower managed care decision makers to appropriately and responsibly manage their chronically ill patient populations, while reducing overall healthcare costs. As healthcare is rapidly transitioning into a more accountable industry, a collective ambition to improve quality of care and patient well-being is fueling the expansion of clinical programs and healthcare reform throughout the managed care environment. *CDMI Report* strives to achieve excellence in communicating the most effective and pertinent healthcare strategies the industry has to offer. To continue on this path to excellence, the publishers of *CDMI Report* invite our readers to share their innovative solutions to chronic disease management by submitting articles for peer review.

CDMI Report invites article submissions pertaining to the following subjects:

- Accountable Care Organizations and Patient-Centered Medical Homes
- Chronic Disease Management and Education
- Clinical Effectiveness Research
- Clinical Guideline Updates/Reviews
- Compliance/Adherence Programs
- Cost-Benefit Research of Pharmaceuticals and Healthcare Strategies
- Cost-Containment Strategies for Managed Care
- Emerging Industry/Pharmacologic Trends
- Healthcare Reform Analysis
- Health Information Technology
- Innovations in the Managed Care Pipeline
- Literature Review
- Outcomes Data Analysis
- Pharmacoepidemiological Research
- Quality-Improvement Initiatives (HEDIS Measures and Star Ratings)

Disease States of Special Interest:

- Alzheimer's/Aging
- Asthma/COPD
- Cardiovascular Disease
- Diabetes
- Gastrointestinal Conditions
- Obesity
- Osteoarthritis
- Osteoporosis
- Overactive Bladder
- Mental Health
- Pain Management

CDMI

CHRONIC DISEASE MANAGEMENT

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Please send articles for consideration to **TLord@CDMIhealth.com.**

MANAGED CARE NEWSSTAND

More Benefits from Disease Registries

Disease registries may be useful tools to help contain staggering healthcare cost increases around the world. An international study of 13 disease registries in five countries—the United States, Australia, Denmark, Sweden, and the United Kingdom—found that well-managed registries may improve patient outcomes, often at a reduced cost.

The researchers say that by making outcome data transparent, registries allow medical professionals to learn continuously and identify the best clinical practices. Registries may also lead to cost-savings. A hip replacement surgery registry in Sweden, for example, led to significant reductions in the need for follow-up surgeries to replace or repair hip prostheses. The researchers calculated the impact of a comparable registry in the United States and estimated savings of $2 billion out of the total expected cost of $24 billion for these surgeries in 2015.

The researchers say that a growing consensus advocates refocusing reform efforts on value as measured by outcomes relative to costs. This study demonstrates that disease registries may support efforts promoting high-quality and cost-effective medical care.

Source: Larsson S, et al. Use of 13 Disease registries in 5 countries demonstrates the potential to use outcome data to improve health care's value. *Health Aff*. 2011;31(1):220-227.

Patients with Cardiovascular Diseases Fare Better with Primary Care

A new study reinforces the importance of primary care services for patients with cardiovascular disease—the leading killer of men and women in the United States. Researchers conducted a cross-sectional analysis of nearly 22,000 adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2008.

The study evaluated the association between where patients usually receive care and disease prevalence. The researchers also examined patients' self-reported histories of several chronic conditions, including high blood pressure, high cholesterol, and diabetes, and cardiovascular events, including cardiovascular disease, heart attack, angina, coronary heart disease, and stroke.

There were no major differences in the prevalence of diabetes or high cholesterol among patients who typically seek care at private doctor's offices, community-based clinics, hospital outpatient clinics, and emergency rooms (ERs). However, those who did not obtain regular care or who usually sought treatment at ERs were less aware that they had chronic cardiovascular conditions than those who obtained care at other sites. In addition, those who used ERs for regular care were 2.21 to 4.18 times more likely to have a history of cardiovascular events than those who were treated at private physician's offices.

This study reinforces the need to develop programs ensuring that patients access long-term disease management services that will enhance their health and possibly prevent high-cost cardiovascular complications.

Sources: Ndumele CD, et al. Cardiovascular disease and risk in primary care settings in the United States. *Am J Cardiol*. 2011. Epub ahead of print.
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Prehypertension Treatment Slashes Stroke Risk

Previous studies have shown that treatment for high blood pressure reduces stroke risk. Now a new meta-analysis of multiple trials shows that administering blood pressure medications to prehypertensive patients can also reduce their stroke risk.

Case Western Reserve University researchers looked at the results of 16 studies evaluating the effectiveness of various antihypertensive medications in more than 70,000 participants. They found that prehypertensive patients (those with a blood pressure of 120-139/80-89 mm Hg) who took medications to control their blood pressure reduced their stroke risk by an average of 22 percent compared with those who took placebos.

These findings reaffirm the importance of aggressive hypertension therapy, and could have future clinical implications as healthcare professionals evaluate and modify their treatment guidelines for patients with prehypertension.

Source: Sipahi I, et al. Effect of antihypertensive therapy on incident stroke in cohorts with prehypertensive blood pressure levels: a meta-analysis of randomized controlled trials. *Stroke*. Dec. 2011. Epub published ahead of print.

Intensive Diabetes Therapy has Dramatic Impact

Tight control of blood glucose levels as soon as possible after diagnosis with Type 1 Diabetes Mellitus (T1DM) helps preserve kidney function for decades, according to a study funded by the National Institutes of Health that was published in the *New England Journal of Medicine*. The study combines data from the landmark Diabetes Control and Complications Trial (DCCT) conducted from 1983 to 1993 and the Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group.

Researchers compared participants who had conventional diabetes therapy with those who had intensive diabetes therapy with the goal of achieving near-normal blood glucose levels. Conventional therapy at the time involved one to two insulin shots per day with daily blood glucose testing. Those engaged in intensive therapy either had a minimum of three insulin injections per day or an insulin pump with frequent self-monitoring of blood glucose levels. The researchers found that intensive therapy cut patients' long-term risk of developing kidney disease in half.

The study suggests that the early management of blood glucose levels is the key to preventing or delaying kidney problems in patients with T1DM. These measures also may lead to major cost-savings. Kidney failure therapies—including dialysis and kidney transplants—cost an average of $42.5 billion annually in the United States.

Source: The diabetes control and complications trial/epidemiology of diabetes interventions and complications research group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*. 2011;365(25):2366-2376.

Best Rx for Knee Osteoarthritis: Weight Loss and Exercise

Losing weight and exercising can reduce pain by up to 50 percent and improve function and mobility in patients with knee osteoarthritis (OA). Researchers conducted a long-term study to determine the effect that weight loss with and without exercise had on a group of 454 overweight adults with OA.

Participants were asked to lose at least 10 percent of their body weight either through dietary restrictions alone or by changing their diets and exercising. In addition, there was an exercise-only control group. The exercise groups performed at least one hour of exercise (low to moderate walking and resistance training) three days a week. After 18 months, researchers found that the diet and exercise group lost more weight and saw the greatest improvements in pain, function, and mobility when compared with the other two groups.

Encouraging patients with knee OA to lose excess weight and start an exercise program when appropriate gives them no- or low-cost healthcare solutions that may improve their overall health and enhance their quality of life.

Source: Messier S. The intensive diet and exercise for arthritis trial: 18-month clinical outcomes. American College of Rheumatology Annual Scientific Meeting. McCormick Place Convention Center, Chicago, Ill. 6 November 2011. Conference Presentation.

Country's Health Gains Stall

After three years of gains in the country's overall health, there was no net improvement in 2011 because of rising rates of obesity, diabetes, and other chronic conditions, according to America's Health Rankings® — 2011 Edition.

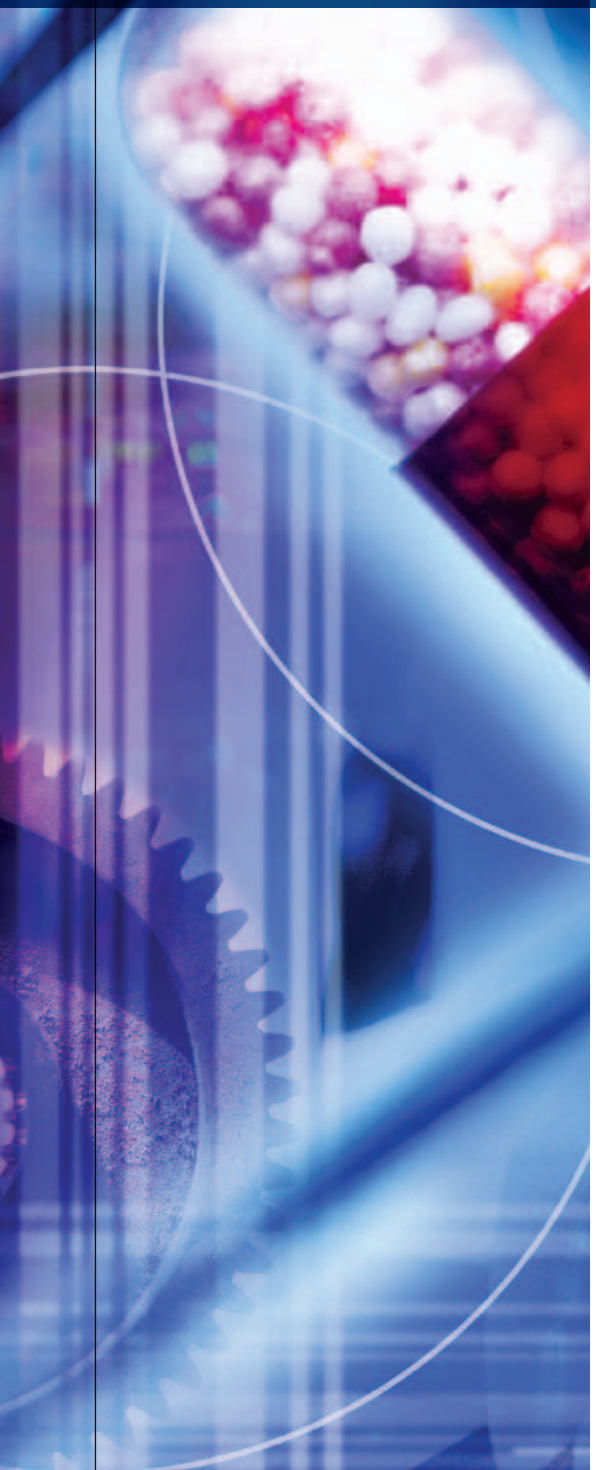
The Rankings, an annual report produced by the United Health Foundation, provides a look at the health of residents in each state based on 23 measures. The report noted several positive trends from 2010 to 2011, as smoking declined 3.4 percent, preventable hospitalizations also went down 3.4 percent, and cardiovascular deaths dropped by 2.8 percent. However, these improvements were offset by other disturbing trends. Obesity rose by 2.2 percent and diabetes jumped 4.8 percent. For the first time, no state in the nation had an obesity rate below 20 percent. In previous reports, America's health improved an average of 0.5 percent each year from 2000 to 2010 and 1.6 percent annually in the 1990s.

The authors note that, without intervention, the trends in obesity and diabetes rates will put additional strain on the country's already burdened healthcare resources. They say that aggressive, data-driven solutions that target preventable chronic diseases can help improve public health.

Source: United Health Foundation. America's Health Rankings® — 2011 Edition. Accessed 14 February 2012 at **www.americashealthrankings.org/SiteFiles/Reports/AHR%202011Edition.pdf.**

Lessons in Pain: A Health Plan's Integrated Approach to Opioid Management

Nicole Dawley, RPh; Brian Moser, RN; Mary Cay Humphreys, RN, MSN; and Mona Chitre, PharmD, CGP



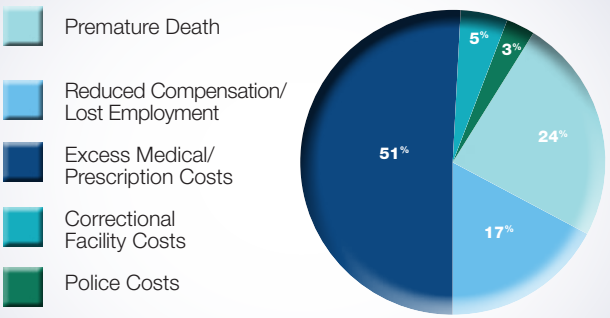
Pain is one of the most common reasons that Americans seek medical care, with approximately 30 percent of the U.S. population diagnosed with a chronic pain condition.[2] Living with chronic pain can negatively impact an individual's job performance, sleep habits, relationships, hobbies, and quality of life. Proper treatment of pain is essential in order to ensure that patients can resume an active lifestyle as quickly as possible. Physicians want to prescribe the appropriate medications to alleviate pain, but sometimes have concerns about prescribing a potentially addictive opioid. Health plans and physicians struggle to balance the treatment of chronic pain while also being vigilant and aware of the potential misuse of pain medications.

The misuse of opioid medications, which are a common treatment for pain, continues to rise in the U.S. The number of patients overdosing on opioids has reached epidemic levels. Patients often begin using these medications for legitimate pain control, but, in some cases, continue using opioids to achieve a drug high even after the initial pain has subsided. Emergency room visits for opioid misuse doubled from 2004 to 2008, and unintentional overdoses have replaced motor-vehicle accidents as the leading cause of accidental death in 15 states.[3] Recreational abuse has led to a 300 percent surge in the sale of medications like oxycodone, hydrocodone, and methadone since 1999.[4] For every one person who is addicted to heroin, there are two people who are addicted to prescription opioids.[5] The cost of prescription opioid abuse represents a substantial and growing economic burden for society. One study examined direct healthcare costs from 1998 to 2002 for commercially insured beneficiaries who had at least one prescription insurance claim. The study found that the average annual cost per capita for opioid abusers was $16,000, compared to $1,800 for non-abusers.[6]

How have communities addressed the issue of opioid addiction? In the past, individuals who wished to break their addictions were hospitalized in inpatient detoxification programs for five to seven days. However, this process is associated with high costs; varying degrees of quality and success; poor discharge planning and follow-up; and requires patients to leave the comfort of their homes and, often, the support of their families. Clearly, communities need a better way to identify potential opioid abusers, help them manage their pain, and counsel the physicians who struggle to find the balance between undertreating and overtreating pain.

In 2007, Excellus BlueCross BlueShield (Excellus BCBS) developed a management initiative to address these very issues. This comprehensive campaign was built on utilizing health plan claims data and providing additional tools and resources to help physicians and patients appropriately manage chronic pain. These resources were designed to help providers engage, empower, and collaborate with members in order to safely treat pain, reduce the misuse of opioids, and treat those in need of detoxification in a safe and cost-effective manner. Early in the conceptualization process, Excellus BCBS determined that the program would need to be multifaceted and integrate many internal healthcare stakeholders so it could maximize the out-

Fig. 1 **Societal Impact of Prescription Opioid Abuse by Category, % of Total Cost[7]**



The increasing prevalence of abuse suggests an even greater societal burden in the future. The total U.S. societal costs of prescription opioid abuse were estimated at $55.7 billion in 2007 (USD in 2009).[7,8]

reach and outcome. Stakeholders included customer service, provider relations, behavioral health, fraud and abuse, medical directors, and pharmacy management.

PROGRAM COMPONENTS

I. Identifying Patients at Risk

The program is based on a trigger report and subsequent prescriber summary. This is the first step in identifying at-risk patients while also improving awareness and providing clinical tools to the prescribing clinicians. Many providers who treat these patients are not aware that the patients may also be obtaining opioids from other prescribers. The claims query is based on specifications from the Drug Enforcement Administration (DEA) that outline risky medication behaviors, as well as a consensus from the health plan team.

Members who meet all three of the triggers below are listed in a prescriber summary:

- More than 90 days of opioid therapy in a 180-day time frame
- Prescribed opioid therapy by three or more prescribers
- Received opioid prescriptions at two or more pharmacies

II. Provider Support

Prescriber Summary (trigger reports): The prescriber summary is generated for each provider to include every patient that meets the previously identified triggers. The summary includes patient-level detail, including drug name, date of fill, individual prescribers, dispensing pharmacy, and associated quantities and days supply. Each provider who prescribed an opioid to a specific patient is included in this report and contacted by the healthcare team. This ensures that all of the relevant providers are aware of the patient's complete opioid history. Prescribers report that this is one of the most impactful pieces of the prescriber summary.

The packet also includes information on how to access clinical tools for the treatment of pain. In conjunction with community experts, the health plan worked to create The Community Principles of Pain Management (CPPM)* guidelines. These guidelines were developed to help advise providers on how to assess and treat pain, and included a number of therapeutic and non-therapeutic options.

Health Plan Support: The health plan team did not want to send the mailing as a stand-alone to providers without giving these clinicians the opportunity to discuss the findings that were incorporated into their provider-specific summaries. Thus, all providers had the opportunity to speak with a pharmacist from the health plan to confirm utilization information, discuss treatment plans, and ask further questions. Support staff triaged calls and connected providers with the appropriate contacts. A clinical pharmacist with expertise in pain management was available if a more detailed follow-up was needed. Table 1 highlights some of the outcomes from these callbacks.

Table 1 **Outcomes from Physician Callbacks**

Providers who claimed they did not prescribe the medication listed generated the highest volume of callbacks. Most of these claims were the result of incorrect billing by the pharmacy.*
Multiple employees from various offices were calling in illegal prescriptions for themselves under the physician's name.**
Providers determined that blank prescriptions were stolen from the office and prescriptions were being obtained fraudulently.**
Providers informed the health plan that based on the mailing, they performed a random drug screen on the patient. Negative results suggested that the patient was diverting.
Providers testified that the summary was a helpful reporting tool for outpatient methadone and Suboxone® patients.

*Pharmacies were contacted to correct billing errors, and the importance of billing correctly was addressed in pharmacy bulletins.
**These cases were referred to the special investigation unit for further follow-up.

III. Suboxone® Initiative

Suboxone® (buprenorphine and naloxone) was approved in October 2002 for the treatment of opiate addiction. Buprenorphine is a partial agonist at the mu opioid receptor, while naloxone is an antagonist at this receptor. The Drug Abuse and Treatment Act (DATA) allows for the use of Suboxone® sublingual tablets and films, which are opioids themselves, for the treatment of opioid

**Dr. Patricia A. Bomba, Vice President and Medical Director, Geriatrics, is the chair of the Community Principles of Pain Management workgroup.*

addiction. This is the first prescription opiate medication approved to prevent withdrawal symptoms and to treat opioid addiction on an outpatient basis. Doctors must undergo a special course in addiction treatment and become registered in order to prescribe this medication, and, per the DEA, physicians are limited to 100 Suboxone® patients at a given time. There is currently a shortage of physicians in Upstate New York, where Excellus BCBS is based, who can prescribe this drug.[9] A strong Suboxone® program may be able to curtail the amount of opioid abuse, and also help those who are addicted to opioids receive outpatient treatment at the appropriate level of care. Additionally, there can be significant economic implications with the use of Suboxone®. A 2008 study of patients with a history of prescription opioid abuse showed that the opioid drug cost, including the cost of Suboxone®, was 26.9 percent less expensive for patients who were using buprenorphine/naloxone versus patients who were not.[10]

One of the goals of the health plan's program was to increase access to outpatient detoxification therapy and to eliminate unnecessary, and sometimes ineffective, inpatient opioid detoxification. Now, members can have symptoms of opiate withdrawal managed safely and effectively without hospitalization. Members can turn to a local primary care physician (PCP) who is certified to administer Suboxone® for opioid addiction or to a nearby outpatient provider for treatment with Suboxone®. With a referral to an outpatient chemical dependence treatment center, patients can now manage their withdrawal symptoms in the comfort of their own homes and incorporate the support of their families into the treatment process.

The benefits of the Suboxone® Initiative are dramatic, and include safe care; an immediate connection and subsequent relationship with certified professionals; and significant cost-savings.[7] Outpatient detoxification costs the health plan less than $300/day on average (excluding medication costs), while an inpatient stay can cost up to $1,200/day. One skeptical provider on a phone review said, "Well, this Suboxone® Initiative is one thing you insurance types got right." Another physician stated, "I've never seen anything like it in my 38 years of practice. Becoming a Suboxone® provider has really opened my eyes to opioid addiction. I can't believe how many people are in need of treatment, and now I can help them in my office."

In order for the goal of outpatient detoxification to become a reality, the Excellus BCBS behavioral health division took a leadership role in identifying the barriers to providing appropriate opiate addiction therapy and creating solutions to improve the region's ability to manage opiate addiction in the outpatient setting. Significant discussions with internal and external stakeholders led to the following actions:

- Increasing the fee schedule for the three-visit induction phase of Suboxone® in the outpatient setting by well over 200 percent
- Proactively recruiting more than 100 certified physicians and 50 outpatient chemical dependency providers to participate in the Suboxone® Initiative
- Eliminating preauthorization for outpatient treatment of opioid addiction with Suboxone®
- Allowing participating PCPs to self-refer when the member is not their own patient
- Establishing open communications with physicians and providers to ensure safe administration protocols for Excellus BCBS members at the appropriate level of care, and the continuity and coordination of care between these providers and the members' PCPs and necessary specialists
- Enabling real-time communications with the provider relations teams and customer service divisions to ensure that they are aware of access to participating Suboxone® providers and outpatient chemical dependency clinics who are accepting new patients. This encourages physicians and provider systems to quickly refer and/or allow patients to triage themselves to the appropriate level of care when calling to inquire about treatment for opioid addiction.

IV. Formulary Management

The health plan formulary was also aligned with the opioid program and its goals of reducing the misuse of these products and decreasing the supply of inappropriate opioids in the community. Studies have demonstrated that the dose of opioids is directly correlated with both fatal and non-fatal overdose.[11] As the opioid dose is increased, patients are placed at a greater risk of overdose. On the Excellus BCBS formulary, all brand and generic long-acting opioids have an instituted quantity limit that ranges from 30 pills to 120 pills per month, depending on drug and formulation. Fentanyl patches have a quantity limit of 15 patches per 30 days. Prior authorization was added to short-acting fentanyl products (Actiq® and Fentora®), restricting use to only cancer-related pain.

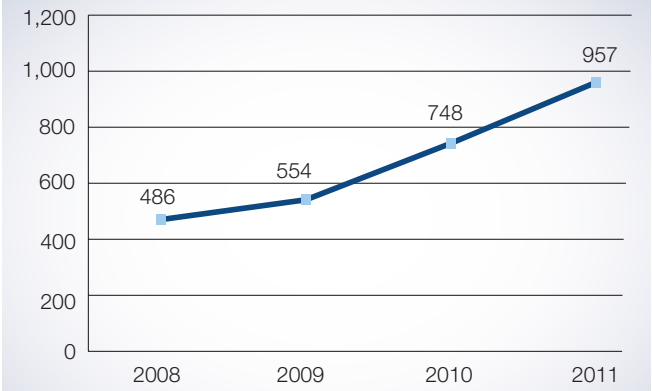
Initial formulary placement of Suboxone® was in tier 3. Because Suboxone® is sometimes prescribed in smaller supplies that require multiple copays per month, addiction specialists were concerned that higher out-of-pocket costs associated with Suboxone® therapy could result in failure of therapy and subsequent relapse. In 2007, Suboxone® tablets were moved to tier 2 in order to provide better patient management. Methadone is also available as a tier 1 generic medication.

Results

The opioid management initiative has had a positive and tangible impact on the community.

- In general, there has been a 3 percent decrease over time of patients hitting the opioid misuse triggers.

Fig. 2 **Suboxone® Utilization, Average Member Counts, 2008-2011**



Graph represents the commercial membership utilization of Suboxone® for Excellus BCBS.

- Patients who were previously identified by the trigger report were not identified as being at risk of misuse on subsequent reports 77 percent of the time. This indicates that providers have altered their prescribing practices, facilitated discussions with patients and/or other providers, or altered pain management (e.g., changed therapy to non-opioid treatment options). (Note: There is awareness that if the patients do not use the health insurance system or pay cash for opioid prescriptions, the claims data and subsequent outreach and results will be compromised.)
- The health plan has seen a decrease in inpatient detoxification by 10 percent over two years (2009-2011).
- The health plan has seen an increase in patients utilizing Suboxone® treatment. See Figure 2.

Additionally, Excellus BCBS conducted a survey to gauge the physicians' responses to the opioid management program. The survey was sent to more than 1,000 prescribers with a 33 percent response rate.

- 88 percent of the respondents found the mailing helpful.
- 61 percent of the respondents found that twice-yearly mailings were sufficient; 32 percent requested that it be mailed more frequently.
- 81 percent of the respondents agreed or strongly agreed that the information helped with their prescribing decisions.
- 41 percent of the respondents contacted someone in response to the mailing, i.e., other prescribers, the health plan, the member, or a dispensing pharmacy.
- 30 percent of the respondents stated that the following tools would be useful for managing patients: Case management; pain management education; disease management resources for the patients and pain clinic contacts; and written pain contracts.

Based on survey results, the opioid letter was revised in order to point prescribers toward a corporate website full of helpful resources, such as the Principles of Pain Management, sample pain contracts, and additional information on outpatient detoxification.

Conclusions

Pain management and subsequent opioid misuse and abuse have a tangible impact on employers, families, and society. Through the Opioid Management Initiative, Excellus BCBS has become a valued resource for providers and patients who require adequate pain treatment. This initiative brought together an integrated cross-functional team of stakeholders in order to address the many far-reaching impacts of opioid abuse. Together, they created an innovative program that helps identify potential abusers, provides resources for physicians to help treat those abusers while also treating legitimate cases of pain management, and reduces the amount of opioids in the community. Through patient and provider feedback, Excellus BCBS will continue to expand the program offerings to meet the needs of the stakeholders in the communities it serves.

Acknowledgements

The authors would like to acknowledge the team that helped to make this program a success: Donald Hunter, Linda Cotton, Dr. Marybeth McCall, Meg Paris, Dr. Patricia Bomba, Dr. Eugene Schneider, Dr. Ann Griepp, Kellie Donovan, Joseph Sauer, and Yanju Yu.

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Staying Above the Stars: Improving Quality Performance Measures for ACE Inhibitors and ARBs

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In the United States, approximately 27 percent of adults ages 65 and older have been diagnosed with diabetes.[1] Unfortunately, the prevalence of Type 2 Diabetes Mellitus (T2DM) in this patient population is projected to increase over the next 20 years.[2-4] Because the majority of these patients will be enrolled under a Medicare plan, the U.S. government will be responsible for a large portion of the associated healthcare costs. In 2007, the American Diabetes Association (ADA) estimated that the total economic cost of diabetes in the U.S. was $174 billion.[5] With the increasing prevalence and the extensive economic burden associated with diabetes, it is not surprising that the Centers for Medicare & Medicaid Services (CMS) placed such a high importance on the treatment of diabetes when revising its Five-Star Quality Rating metrics for 2012.

Among other modifications, CMS has made several interesting additions to the quality measures within the "Drug Pricing & Patient Safety" domain. These ratings evaluate the quality of care provided by Medicare Part D plans, including Medicare Advantage Prescription Drug (MAPD) plans and stand-alone Prescription Drug Plans (PDPs).

Specifically, the additional metrics correlate with medication adherence to HMG-CoA reductase inhibitors (statins), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and four categories of oral diabetes medications. These adherence measures, which are quantified based on the proportion of days covered (PDC), complement the medication safety metrics that have been incorporated into the star ratings since 2008, such as high-risk medications in the elderly and the appropriate treatment of hypertension in persons with diabetes. The medication safety metrics that have been incorporated into the ratings since 2008 have been a major obstacle for health plans; the new adherence metrics will certainly bring additional challenges.

Further propelling the importance of the medication safety and adherence metrics is the weighted measurements in the 2012 revisions. Each metric is based on a weighted factor between one and three, meaning the different measures do not contribute equally to a health plan's overall star rating. The five clinical and patient safety measurements, which include those related to ACE inhibitor and ARB use, have been assigned the highest weighted value (see Table 1 for Medicare Part D weightings). This new measurement system could significantly influence the overall star ratings for many insurance providers.

Table 1

2012 Weighting for Medicare Part D Measures

Measure ID	Measure Name	Weight in Medicare Part D Star Ratings
D01	Call Center – Pharmacy Hold Time	1.5
D02	Call Center – Foreign Language Interpreter and TTY/TDD Available	1.5
D03	Appeals Auto-Forward	1.5
D04	Appeals Upheld	1.5
D05	Enrollment Timeliness	1.0
D06	Complaints about the Drug Plan	1.5
D07	Beneficiary Access; Performance Problem	1.5
D08	Members Choosing to Leave the Plan	1.5
D09	Getting Information from Drug Plan	1.5
D10	Rating of Drug Plan	1.5
D11	Getting Needed Prescription Drugs	1.5
D12	MPF Composite	1.0
D13	High-Risk Medications	3
D14	Diabetes Treatment	3
D15	Part D Medication Adherence to Oral Diabetes Medications*	3
D16	Part D Medication Adherence for Hypertension (ACEI/ARB)*	3
D17	Part D Medication Adherence for Cholesterol (Statins)*	3

*New quality metric for 2012

Source: Centers for Medicare & Medicaid Services. Medicare Health & Drug Plan Quality and Performance Ratings 2012 Part C & Part D Technical Notes. October 2011.

With the 2012 revisions, ACE inhibitors and ARBs are garnering a substantial amount of attention from health plans. There are now two heavily weighted metrics that are based solely on the use of these agents. Appropriate treatment of hypertension in persons with diabetes requires that patients who have been determined via prescription drug encounter (PDE) data to have both diabetes and hypertension fill at least one prescription for either an ACE inhibitor or an ARB during the measurement year. New for the 2012 ratings is the Part D medication adherence for hypertension metric. This measurement uses PDC to quantify adherence rates to ACE inhibitors and ARBs among the health plan's coverage network. Since each of these metrics holds the highest possible weighting, it is in the health plans' best interest to promote early initiation of these medications within their diabetic and hypertensive patient population and improve medication adherence and persistence in all patients prescribed an ACE inhibitor or an ARB.

It is important for health plans to understand that these two ratings are not mutually exclusive. Although plans will have to report separate measurements for these metrics in 2012, the members contributing to the success of these performance ratings will overlap. For the first metric, appropriate treatment of hypertension in persons with diabetes (D14), the goal is to initiate the appropriate ACE inhibitor or ARB therapy in patients identified to be diabetic and hypertensive who are not currently utilizing one of these agents. However, once a patient is successfully initiated on ACE inhibitor or ARB therapy, the health plan is now responsible for ensuring these patients demonstrate medication persistence in order to comply with the second metric, Part D medication adherence rates to ACE inhibitors and ARBs (D16). Clinical programs designed to improve a health plan's star rating in these categories should be developed in tandem and implemented with the goal of initiating ACE inhibitor or ARB therapy in the appropriate patients and strive to promote medication persistence. For these metrics, the term "adherence" is used synonymously with appropriate medication initiation and continued persistence to ACE inhibitor and ARB therapy.

Clinical and Financial Benefits of ACEI/ARB Therapy in Patients with Diabetes

The appropriate utilization of ACE inhibitors and ARBs in patients with diabetes and hypertension is one quality met-

ric that health plans should target in order to improve their performance rating. Hypertension is one of the most common comorbidities in patients with diabetes, and both hypertension and diabetes are risk factors for developing chronic kidney disease (CKD) and microvascular complications. Appropriate early initiation of an ACE inhibitor or an ARB offers several therapeutic advantages in this patient population beyond the traditional salutary effects on blood pressure. Specifically, these medications can provide prolonged renal protection and reduce the risk of end-stage renal disease (ESRD) by up to 50 percent and the risk of microvascular complications by one-third.[10-17] This is reflected in national diabetes management guidelines, such as those published and updated annually by the ADA; these recommend that, in the absence of contraindications, non-pregnant patients with diabetes and hypertension and/or micro- or macroalbuminuria should be placed on either ACE inhibitor or ARB therapy.[2]

In addition to the medical benefits these medications can provide, there is evidence that they can result in significant cost-savings for employers, managed care plans, and public payors. A study published in the *Annals of Internal Medicine* evaluated the cost-effectiveness of ACE inhibitors in Medicare beneficiaries with diabetes. The study analyzed the clinical and financial implications of providing beneficiaries with ACE inhibitor therapy free of charge and compared the results to a traditional cost-sharing model. The authors used a Markov model that mimicked the natural history of renal and cardiovascular complications in diabetes and the risk reduction possible with ACE inhibitors, along with actual rates of ACE inhibitor utilization based on NHANES 1999-2000 utilization of 40 percent in this population. They found that a 20 percent increase in utilization would reduce not only mortality but also total Medicare costs (0.23 quality of life years and $1,606 per beneficiary). The cost-savings resulted from fewer medical events and was significant even when considering the higher cost of the medications and future healthcare costs unrelated to diabetes.[6]

A later study conducted after Medicare Part D was implemented found similar outcomes. Over three years, even a 10 percent increase in adherence to a renin-angiotensin-aldosterone system (RAAS) inhibitor in patients with diabetes reduced payor medical costs by $285 per patient.[7]

Barriers to Adherence

Unfortunately, despite the proven medical benefits and the cost-savings associated with ACE inhibitors and ARBs, both patient adherence to therapy and physician adherence to best-practice guidelines remain inadequate. A managed care registry identified diabetic patients with comorbid hypertension and/or albuminuria and found that 83 percent of patients had hypertension, albuminuria, or both, making these patients appropriate candidates for ACE inhibitor or ARB therapy. However, only 61 percent of the identified candidates were currently receiving a recommended medication.[7]

Non-adherence to therapy is costly, primarily because of the negative impact it has on overall outcomes. In one study of Medicare Part D enrollees with diabetes who had filled at least one prescription for an ACE inhibitor or an ARB, 46 percent were non-adherent and 6.3 percent of these patients had experienced a potentially avoidable hospitalization.[8]

As noted earlier, Medicare prescription plans are now required to track and monitor ACE inhibitor and ARB therapy in patients with diabetes and hypertension as a quality performance measure. In 2011, many Medicare plans struggled to improve their star rating in this category. During this measurement year, the average MAPD and PDP ratings for this metric (at least one prescription for an ACE inhibitor or an ARB in patients with diabetes and hypertension) were less than three stars, 2.94 and 2.87 respectively.[9] Table 2 shows the percentage of members within MAPDs and PDPs with diabetes and hypertension that will need to be on the appropriate ACE inhibitor or ARB therapy in order to achieve specific star ratings in 2012.

Table 2 — 2012 Medicare Part D ACE Inhibitor/ARB Benchmarks for Patients with Diabetes and Hypertension

	Star Rating	Benchmark*
Prescription Drug Plans	5	>=83.9%
	4	>=83.0% to <83.9%
	3	>=81.8% to <83.0%
	2	>=80.9% to <81.8%
	1	<80.9%
Medicare Advantage Prescription Drug Plans	5	>=87.3%
	4	>=86.0% to <87.3%
	3	>=83.2% to <86.0%
	2	>=81.5% to <83.2%
	1	<81.5%

*D14: Using the Kind of Blood Pressure Medication that Is Recommended for People with Diabetes

Source: 2012 Measure Data: Medicare Part D Report Card Master Table

Table 3 Patient-Related Reasons for Non-Adherence

Knowledge	• Patients' lack of understanding • Underestimating the consequences of non-adherence • Patients are unclear as to how and when to take medications or adhere to treatment
Attitude	• Embarrassment or pride • Desire to save money • Cultural beliefs
Current Health Status	• Lack of adherence when asymptomatic • Belief that medications are contributing to worsening health • Side effects or fear of side effects • Memory impairment
Support	• Lack of a support system to prompt, remind, or assist patients to appropriately adhere to therapy
Literacy	• Cannot read or properly interpret instructions • Do not understand which medications are for which conditions
Access	• Unable to access pharmacy for fills/refills • Health plan formulary availability • Cost

Source: MTS Medication Technologies. The reasons for non-adherence. Accessed 27 February 2012 at **www.mts-mt.com/learning/medication-adherence/the_reasons_for_non_adherence.**

Lack of adherence can be attributed to both patient- and physician-related variables. Patient-related adherence challenges tend to revolve around knowledge, attitudes, current health status, support, literacy, and access (Table 3). Many patients, especially those 65 years of age and older, fall into several of these categories. Perhaps the most pervasive challenge that faces managed care plans and healthcare providers is that addressing patient-related adherence problems requires a multifaceted approach and individualized action plans; there is no "magic bullet."

However, addressing barriers to physician adherence is just as challenging, and is often overlooked by health plans as a method to improve medication adherence. Physician-related adherence challenges include a lack of education on, or appreciation for, the current best-practice guidelines. Physician "buy-in" to best-practice guidelines can be a problem within complicated disease states, including diabetes, as these recommendations are often developed through the compilation of "expert" opinions. Physicians may not support the recommendations delivered in these consensus statements and, thus, treat their patients as they feel is appropriate. Other physicians may simply be unaware that ACE inhibitors and ARBs are the recommended therapy for patients with both diabetes and hypertension.

Physicians also may contribute to adherence problems by not following up with patients to ensure that they understand their medication regimens and by not scheduling enough time for appointments to discuss potential medication-related problems. One analysis of physician-related barriers to medication adherence concluded that the quality of the doctor-patient relationship was one of the most important factors impacting patient adherence.[10]

Additionally, many of these complicated diabetic patients are referred to an endocrinologist, nephrologist, and/or cardiologist. If the primary care physician is not appropriately coordinating care between all treatment sites, the role of each specialist may not be clearly defined and prescriptions may be duplicated or completely omitted from the patient's therapy.

It is also important for physicians to understand medication contraindications specific to ACE inhibitors and ARBs. For instance, while angioedema is a key contraindication, mild renal impairment is not, since these drugs are nephroprotective. Thus, it is important that plans educate their healthcare providers that a slight increase in potassium or glomerular filtration rate is to be expected when initiating ACE inhibitor or ARB therapy. Additionally, many physicians discontinue ACE inhibitor therapy if the patient develops the characteristic dry cough as a result of taking these medications. While this may be appropriate, it is not a contraindication to the use of an ARB, since these medications do not inhibit the degradation of bradykinin. However, many patients who experience the dry cough associated with ACE inhibitors may never be evaluated for appropriateness of ARB therapy.

Strategies to Improve ACEI/ARB Initiation and Persistence

While there is no simple method to improve adherence to ACE inhibitor or ARB therapy, a multidimensional program addressing the problem from several angles can make a significant difference. Health plans that proactively assess the problem of adherence on both the physician and patient levels seem to generate the most success.

One large Blue Cross plan has implemented a telephonic outreach program designed to improve physician prescribing habits and adherence to best-practice guidelines. The plan starts by identifying members with diabetes and hypertension from prescription claims data, calling the physician office to

identify a point of contact (often a clinical assistant or nursing manager), and, depending on the time available, discussing the patient-specific information on that call. The caller, usually a pharmacist, faxes a letter that includes information about the patient and the preferred medication based on the plan's formulary. It also includes a simple form for the physician to complete and return to the plan that specifies which medication the patient will be, or has been, initiated on or why ACE inhibitor or ARB therapy is not appropriate. If the patient is not taking an ACE inhibitor or an ARB, but there is a good reason (e.g., contraindication), it is documented and that patient is then removed from future call lists. The form also includes a scaling question about the usefulness of the information provided and provides space for additional comments. This personalized approach, while more time consuming, is far more effective than simply sending a "Dear Doctor" letter, as many plans do.

The plan then takes the information it receives from the physician and acts upon it appropriately. For instance, if the reason for non-adherence is lack of knowledge about the guidelines, the plan provides education to the physician. If the problem is that the patient has not been seen in nine months, the plan recommends scheduling a visit. Many times, patients refuse the physician's recommended therapy. If this is the situation, a medication therapy management (MTM) pharmacist follows up directly with the patient to provide educational support and to identify the factors influencing the patient's refusal. This integrated approach and additional patient outreach has proven very successful when attempting to initiate diabetic patients on the appropriate hypertensive therapy.

The most successful plans use such an integrated approach, said Christine Leyden, Chief Accreditation Officer for the Utilization Review Accreditation Commission (URAC) in Washington, D.C. URAC tracks ACE inhibitor and ARB prescriptions as a quality indicator by addressing adherence for both patients and physicians. It starts by monitoring adherence through the pharmacy benefit to track prescriptions and refills. Once a prescription is initially filled, there is an opportunity for the disease management team to follow up with both the patient and the physician in order to improve persistent and appropriate therapy.

One plan with which Leyden works checks in with its patients on a quarterly basis. Patients with poor compliance receive a call and education from a pharmacist; if they have other chronic conditions, they are enrolled in a case management program.

Leyden said that it is critical that patients and physicians work as a team to stress medication adherence. At the same time, she said, plans need to provide the necessary resources for physicians to improve adherence and to understand the barriers preventing patients from using the drugs appropriately.

One option that plans might want to consider is mimicking the Patient Centered Healthcare Home program that URAC has developed. In this program, the patient is responsible for seeing a specific physician at every visit, and the healthcare provider is responsible for educating the patient about his or her medications and assessing barriers to adherence. "Doing aggressive outreach to the patient so that they understand the need for the medication, why it's important, and how to take it is essential," Leyden said.

RegenceRx, an Oregon-based prescription benefit plan, has several contracts subject to the CMS Star Ratings. Each of the RegenceRx contracts received either 4.5 or 5 stars for the ACE inhibitor and ARB prescriptions in patients with diabetes and hypertension metric in 2011. While the percentages vary among the different contracts, all are trending several percentage points higher than the national average, said Director of Pharmacy Services Lynn Nishida, RPh.

RegenceRx structured its MTM program to include disease states that it knew would be targeted for adherence, Nishida said. Thus, the plan is able to identify patients with diabetes and hypertension and reach out to individual members, whether through mailings, electronic communication, or, in some cases, calls from pharmacists who are trained to identify barriers to care and opportunities to improve adherence.

RegenceRx can also call the physicians and provide them with the names of patients within their practices who may be appropriate candidates for the therapeutic intervention. In addition to the patient names, the plan can also provide the physicians with patient medical and prescription histories. "We heard from physicians that they don't want generic letters; they want us to identify the patient who would benefit from the therapy," Nishida said. The letters also warn of any potential drug/drug interactions or adverse events that may have been identified for specific patients.

The pharmacist calls to patients are particularly effective, Nishida said, since the pharmacist is empowered to act on reducing barriers. For instance, if cost is a barrier to adherence, the pharmacist works with the member's doctor to switch to a lower-cost medication—possibly a generic. The company also offers a zero copayment for the first fill of certain generic

medications. Studies show that large copayments have a negative impact on adherence, particularly among the elderly.[11-15]

In one study of socioeconomically diverse patients with diabetes, nearly 18 percent of these patients did not use the recommended amount of medications because of cost issues. Those with private insurance, Medicare or Medicaid, and uninsured patients were two to three times more likely to report underuse of medication when compared with patients in the Veterans Administration (VA). Not surprisingly, underuse resulted in significantly more symptoms, poorer physical and mental functioning, and higher HbA_{1c} levels.[16]

There is also strong evidence that pharmacist involvement can improve adherence. A retrospective chart review of patients with diabetes who were seen in a family medicine clinic found that pharmacist interventions (direct consultation and therapeutic education sessions with the provider, as well as patient evaluations) substantially increased guideline adherence. Prior to the intervention, 49 percent of the patients evaluated received appropriate therapy. After implementing the pharmacist-mediated program, that figure increased to 90 percent.[17]

"Our senior population is really appreciative of any type of call from healthcare professionals who care about what's happening with their medication," Nishida said.

Finally, it is important that plans encourage members to use their Medicare drug coverage to fill prescriptions so that their adherence can be tracked. If, for instance, the member fills a prescription at a retail pharmacy because it offers a $4 prescription discount plan, the health plan has no way of tracking the patient's adherence, and will not receive credit from Medicare as a provider of high quality care. By reducing the generic copayment structure of certain medications (i.e., ACE inhibitors and losartan) to $4 or less, health plans can motivate patients to fill their generic medications using their Medicare prescription benefit plans and limit the amount of patient opportunities lost to retail pharmacy discount plans.

Bottom Line

Reimbursement for MAPD plans will drop over the next few years as the Patient Protection and Affordable Care Act (PPACA) is implemented. If MAPD plans want to maintain revenues and competitiveness among Medicare beneficiaries, they should focus on the quality parameters included in the CMS Five-Star Quality Rating system. Now that metrics such as medication adherence for ACE inhibitors and ARBs are weighted, plans should implement programs that specifically focus on these requirements to improve patient outcomes and simultaneously increase their star ratings and bonus potential. Such programs require intensive, individualized interventions with both physicians and patients in order to achieve optimal effectiveness. With the potential for a 5 percent reimbursement on overall Medicare expenditures, the return on investment should be well worth the extra efforts.

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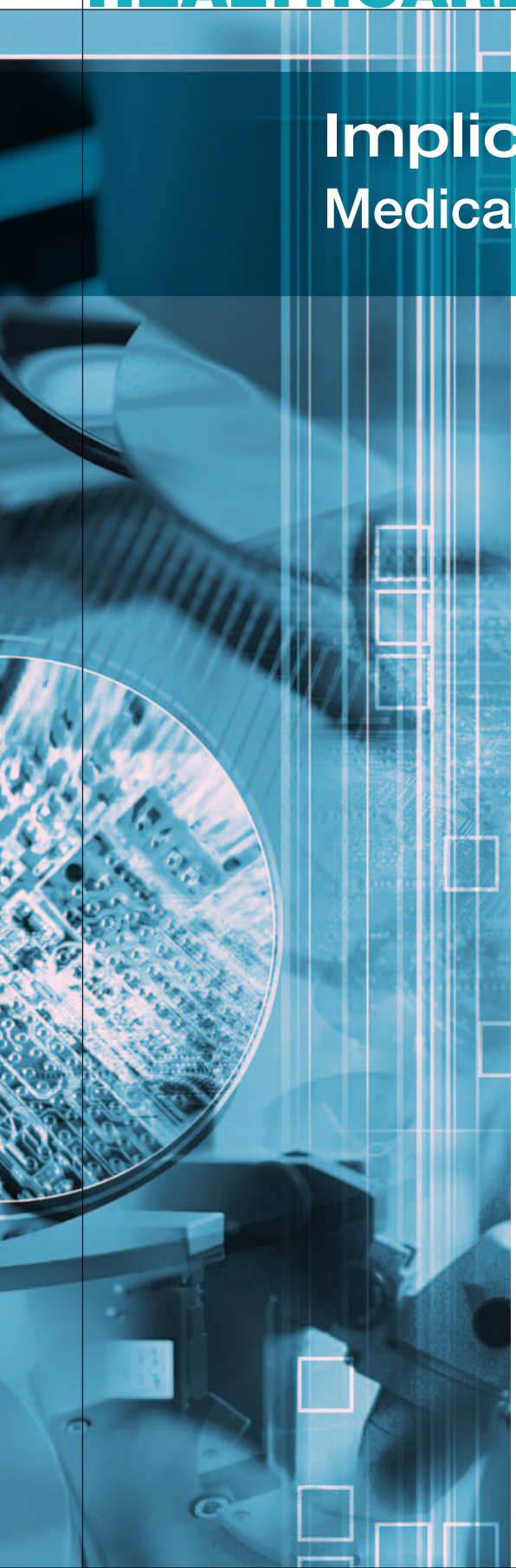

Implications of the Revised Medical Loss Ratio on Managed Care

Maria Lopes, MD, MS, Chief Medical Officer, AMC Health; and Caitlin Rothermel

In December 2011, the U.S. Department of Health and Human Services (DHHS) issued its final rules regarding acceptable medical loss ratio (MLR) expenditures.[1,2] This was in response to a provision in the 2010 Patient Protection and Affordable Care Act (PPACA) that specified the minimum MLR standards for insurance companies. The MLR refers to the minimum percentage of revenue derived from insurance premiums that must be used by payors to fund enrollee medical claims and other medically relevant services. If insurers do not meet the minimum MLR requirements, they will now be obligated to provide premium refunds to their beneficiaries. In addition, new mandatory income and expenditure reporting requirements have been established, and plan-specific reports will be made publicly available by the DHHS (Table 1). The intent of this provision is to increase the financial transparency of private insurance companies, and to ensure that consumers receive adequate value for their premiums through the minimization of administrative costs.[2-4]

Table 1

New PPACA MLR Reporting Requirements[2,4]

The new reporting standards, which became effective in 2011, require insurance companies that issue policies to individuals, small employers, and large employers to report the following information in each U.S. state where they conduct business:

- Total earned premiums
- Total reimbursement for clinical services
- Total spending on activities to improve quality
- Total spending on all other non-claims costs, excluding federal and state taxes and fees

The PPACA method of quantifying the new MLR is slightly different from the previous industry standard. The revised MLR formula allows for healthcare-related activities to improve quality, as well as for the deduction of certain taxes and fees generated from the overall revenue stream. Minimum MLRs also vary based on whether the payor operates in the large-group market (85 percent minimum MLR) or the small-group and individual markets (80 percent minimum MLR).[2,5] However, in the recently released final MLR rule, some of the recommendations proposed by the insurance industry regarding acceptable categories for cost deductions were not incorporated. For example, requests to deduct the services of insurance brokers and agents from MLR-adjusted premiums were denied; these fees will continue to be considered administrative.[2,4]

According to a recent Government Accounting Office (GAO) report, in the three years preceding the implementation of the PPACA, the majority of U.S. insurers' traditional MLR calculations met or exceeded current PPACA requirements.[2] Regardless, payors and researchers have expressed concerns that the new MLR requirements

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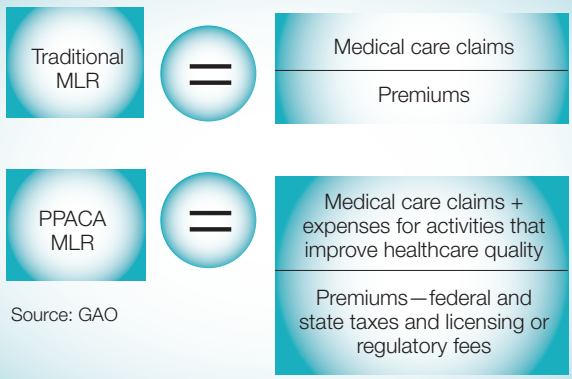
will lead to negative consequences, such as reduced competition and substantial new administrative and reporting burdens.[6-8] The PPACA MLR revisions are intended to improve the clinical management of covered beneficiaries, but if these concerns are accurate, the new requirements may limit the ability to provide cost-effective management services within managed care.

MLRs: Traditional and PPACA

Historically, payors calculated the MLR by dividing medical care claims (numerator) by premiums (denominator). However, the PPACA MLR numerator also includes expenses for activities that improve healthcare quality (Figure 1). The revised denominator includes not only premiums, but all federal and state taxes (excluding taxes on capital gains and investment income), licensing or regulatory fees, and costs associated with clinical effectiveness monitoring and national accreditation management.[2] These changes are based on recommendations made to the DHHS by the National Association of Insurance Commissioners (NAIC), and will lead to MLR calculations that are, overall, more favorable for payors. Insurers who operate in individual, small-group, and/or large-group markets will be required to report separate MLRs for each group, and for each state in which they are licensed to operate.[2,9-11]

Fig. 1 Key Components of Traditional and PPACA MLR Formulas[2]



Source: GAO

Healthcare quality activities considered acceptable for inclusion in the PPACA MLR include those that are grounded in evidence-based practices, based on identified patient need, and designed primarily to "increase the likelihood of desired health outcomes in ways that can be objectively measured."[2,4] Table 2 summarizes the recognized MLR-eligible activities to improve healthcare quality.

Table 2 Acceptable Healthcare Quality Activities for Inclusion in PPACA MLR[2,4]

1. Activities that improve health outcomes
2. Activities that reduce hospital readmissions and/or improve patient safety
3. Efforts to implement, promote, and increase patient wellness and health
4. Activities that enhance the use of healthcare data to improve quality, transparency, and outcomes (including health information technology [IT] expenditures)
5. In 2012-2013, up to 0.3 percent of earned premium costs associated with conversion to the new International Classification of Diseases system (ICD-10) can be considered quality-improvement activities.

Transitioning to the PPACA MLR

Signs are generally positive that many payors will meet the new PPACA MLR targets. In September 2011, in testimony to the U.S. House of Representatives Committee on Energy and Commerce, Lynn Bates Quincy, a senior analyst at the Consumers Union, noted that prior to the federally established PPACA, approximately one-third of U.S. states had already enacted MLR provisions. This has provided the insurance industry with experience in meeting stringent MLR targets.[5] In addition, and as noted earlier, in 2011, the GAO published an analysis of traditional MLR averages from 2006 to 2009.[2] Except for 2006 (small- and large-group markets), the mean traditional MLRs reported by insurers met or exceeded current 80 and 85 percent targets (see Table 3, page 26).

An assessment conducted by the PricewaterhouseCoopers' Health Research Institute in 2009 confirmed that the traditional U.S. MLR has remained relatively stable since 2003, with an average level at or above 80 percent.[12] However, even with strong average scores, substantial MLR marketplace variability exists, particularly in the individual market.[2] According to the DHHS, more than 20 percent of individual market plans spend in excess of 30 cents of every premium dollar on administrative costs.[4]

Meeting the MLR requirements remains a substantial concern for many health plans and, for specific markets, the DHHS is offering temporary reassurance. If legitimate concerns

Table 3 Average Traditional MLRs by Market for Insurers, 2006-2009*[2]

	Individual Market		Small-Group Market		Large-Group Market	
Year	(N)	Mean	(N)	Mean	(N)	Mean
2006	180	84.3	281	79.5	316	84.9
2007	186	83.3	290	81	319	87.3
2008	194	81.2	287	80.6	311	87.3
2009	197	84.7	312	83.1	340	88.8

Source: GAO analysis of NAIC data

*From GAO: Since traditional MLRs were calculated differently than they will be under the PPACA requirements, these data cannot be used to predict what insurers' MLR would have been using the PPACA MLR format.

exist that the new regulations may destabilize a state's individual market and/or inhibit consumer choice in plan selection, the state can request a transitional adjustment for up to three years.[2,4] Currently, more than a dozen U.S. states and territories have applied for such extensions; some have been approved while others are still under review.[2,5] The DHHS also reports that upward MLR adjustments (between 1.2 and 8.3 percentage points) may be made for plans that experience unanticipated claims variability (i.e., those with greater than 1,000 but less than 75,000 life years).[2]

Key Payor Concerns

Since the interim final rule on the PPACA MLR was released in December 2010,[3] payors have expressed concerns that the new requirements might negatively affect day-to-day operations, as well as the bottom line. For example, the highly specific, state-by-state data disaggregation required for PPACA MLR reporting will add an administrative burden that may lead to lower MLRs in some states. This will affect interstate, large-group markets and/or plans operating in more than one state that have historically reported combined MLR data and/or practiced cost-shifting between states.[2,6,13] In 2011, the GAO reported that, due in part to PPACA MLR requirements, one large insurer had exited the individual market in one state and was considering a similar move in other states. However, several other large insurers interviewed by the GAO indicated that PPACA MLR requirements will not affect where they conduct business.[2] It has also been noted that individual insurance companies operating in multiple states may be at a disadvantage if state-by-state enrollment is not uniformly distributed across the entire coverage area. These companies with sparse enrollment in certain states may find it difficult to lower administrative and marketing costs to meet the new MLR requirements.[14]

It can also be expected that tensions will emerge as the range of key MLR stakeholders expands. In the past, investors were the primary consumers of MLR data. Moving forward, the federal and local governments, as well as individual customers, will become equally concerned with MLR outcomes.[13] Moreover, 50 million new customers are set to enter the insurance market by 2014 due to PPACA regulations; the impact this will have is unknown.[7] Research indicates that uninsured U.S. residents tend to be lower-income and less likely to receive comprehensive medical and preventive care when compared with insured individuals.[15] It has been suggested that the volume of newly insured individuals may drive up costs and could potentially have a negative effect on the PPACA MLR.[7] With the anticipated increase of insured Americans entering the market, the insurance companies that can seamlessly provide appropriate coverage to an inflated population of high-risk beneficiaries may have an advantage. The organizations best suited to meet the needs of these newly insured patients, and maintain an appropriate MLR, will most likely be large insurers with the preexisting infrastructure and resources to handle an increase in enrollment.[11]

Over the short term, the insurance industry and independent researchers have identified a number of potential business operation and patient access roadblocks associated with PPACA MLR implementation. Table 4 lists several of these concerns, as well as the available arguments in support of or against the key concerns.

Additionally, it has been acknowledged that the PPACA MLR may spur greater consolidation in the insurance industry, leading to a market dominated by large, for-profit insurers.[2,7,8,10] However, it is too early to assess the validity of these concerns.[8] What is certain is that this is a time of substantial transition for U.S. payors. Companies that can find innovative ways to lower administrative costs and manage portfolio risks are more likely to remain competitive in this new environment, while those who depend on underwriting and have high expense ratios will find it more difficult to thrive.[11] This may also prove to be a period during which multiple new opportunities are identified to provide efficient, proactive care management services targeted toward patients with chronic disease.[7] Adaptability will be the key to surviving the changes brought on by the PPACA MLR regulations.[11]

Table 4 **Insurance Industry Concerns Regarding the Impact of the PPACA MLR[6-8,10,13,16]**

Key Concern	Rationale For or Against Concern
Reduced competition, including substantial barriers to entry for new insurance entities	• Some insurers may leave markets where they have few enrollees. • PPACA MLR regulations may push potential profits too far into the future to make new ventures (i.e., start-up companies) feasible. • Some established companies that currently provide health insurance may leave the market; organizations most likely to depart will be those that offer health insurance as only part of a comprehensive range of insurance types.
Risk that insurance providers will exit individual markets	• It was recently estimated that 29 percent of U.S. individual market insurers might have PPACA MLRs below the 80 percent minimum. If these insurers exit the market, major coverage disruption is possible.
Competitive disadvantages for non-profit payors	• The PPACA MLR requirement constrains an insurer's retained premium income; this potentially limits the insurer's ability to accumulate capital and expand. • For-profit insurers can finance their capital needs by issuing equity shares. However, non-profit insurers have no source of investment capital beyond excess premium income.
Increased patient premiums	• Some insurers may try to raise their premiums to increase the amount retained for overhead and profit; however, it is reasonable to expect that competition and rate review will limit major increases.
Decreased patient access to high-deductible health plans	• High-deductible health plans tend to have higher administrative costs and consequently lower MLRs; this may lead to reduced access.
New reporting burdens and PPACA MLR structure may discourage administrative functions, such as fraud prevention and utilization management	• Insurance companies have a strong incentive to identify fraud, regardless of where it is allocated in the PPACA MLR. • Some insurers have indicated that they will shift from quality-improvement activities not covered in the PPACA MLR formula (such as retrospective utilization review) to alternate approaches that are covered (i.e., prospective utilization review).

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Stimulant Abuse, Misuse, and Diversion: A Growing Problem within Managed Care

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In a world in which sleep deprivation and multitasking have become synonymous with success, it is no wonder that more Americans are turning to prescription stimulants—in addition to highly caffeinated drinks—to promote wakefulness and concentration.

This trend, however, poses challenges for managed care plans trying to control their continually escalating prescription drug expenditure. Many of these stimulants are used off-label or diverted to individuals without prescriptions. One study estimated that the diversion of stimulant medication used to treat attention deficit hyperactivity disorder (ADHD) costs U.S. health plans $8 million each month. Diversion accounted for approximately 3.6 percent of the total costs that private health plans paid for ADHD medications.[1]

New guidelines from the American Academy of Pediatrics that outline the best-practice recommendations for the diagnosis and management of adolescent ADHD may contribute to the potential for diversion. These guidelines may increase the prescribing of prescription stimulants in the adolescent and college-age patient populations, both of which are notorious for diverting their stimulant medications.[2-5]

Increasing Prevalence of ADHD Correlates with Stimulant Diversion

In the United States, nearly 10 percent of children ages 4 to 17 have been diagnosed with ADHD. This percentage seems to rise throughout adolescence with 11 percent between ages 11 and 14, and 13.6 percent between ages 15 and 17. Most of these children—an estimated 2.7 million—are prescribed medication used to treat this disorder, with patients ages 11 and older up to 71 percent more likely to be prescribed stimulants than their younger peers.[6] In addition, approximately 5 percent of adults have been diagnosed with ADHD, many of whom are also prescribed stimulant medications such as methylphenidate and amphetamines.

In one analysis of privately insured individuals with ADHD ages 18 to 49, an estimated 16.6 percent diverted their medication.[1] Other studies found that up to

26 percent of college students prescribed methylphenidate gave away or sold their medication. Another analysis of data collected via personal interviews with 483 college students ages 17 to 19 found that nearly 62 percent of students who were prescribed a stimulant medication admitted to diverting it at least once.[3,7]

Teenagers are not the only ones diverting their ADHD medication; a quantitative study of 66 adults prescribed methylphenidate for their ADHD found that 44 percent diverted it and nearly a third admitted to using the drugs other than prescribed.[8]

While the primary problem with ADHD stimulant medications is diversion, the challenge with the newer stimulants, Provigil® (modafinil) and its younger sibling, Nuvigil® (armodafinil), is off-label use for jet lag and to promote alertness. Currently, these products are approved only for narcolepsy, excessive sleepiness associated with obstructive sleep apnea, and shift-work sleep disorder. In addition, because they are schedule IV drugs, prescriptions are easier to obtain and refill than those for ADHD stimulants, which are schedule II.

The *New York Times* recognized the potential for off-label use of Provigil® in 2004: "As modafinil grows more widely available, it is becoming a fixture among college students, long-haul truckers, computer programmers and others determined to burn the midnight oil."[9]

The drugs are also used off-label for fatigue in multiple sclerosis (MS), Parkinson's disease, and some autoimmune conditions.[10] Although there are no published studies on the costs of off-label use of Provigil® or Nuvigil® to managed care organizations, at roughly $14 per tablet for Nuvigil® and $20 per tablet for Provigil®, it is clear that inappropriate use can have a significant impact on a health plan's pharmaceutical budget.

Massive Promotions

While Cephalon, the manufacturer of Provigil® and Nuvigil®, cannot promote the drugs' off-label use, it can fund non-branded advertising about fatigue. *Bloomberg Businessweek* reported in August 2011 that Cephalon was building awareness for shift-work sleep disorder through non-branded radio ads as part of its $3.6 million Nuvigil® promotional budget.[11] One managed care executive said he frequently heard these advertisements placed over early morning airwaves, and felt they were designed to appeal to long-haul truckers as a way to promote alertness.

The investment is paying off. Since the product launch in 2009, Nuvigil® has experienced a 50 percent annual sales growth, with sales of $186 million in 2010. Analysts estimate that the sales could reach $577 million by 2015.[11] With the launch of Nuvigil®, Cephalon also raised the price of Provigil®, which is scheduled to lose patent exclusivity in 2012. In 2011 alone, Cephalon increased the wholesale acquisition cost (WAC) of Provigil® by more than 46 percent.[26] The *Businessweek* article noted that the price increase was designed to persuade patients and managed care organizations to switch to the newer agent that retains patent longevity.

There remains the possibility that Cephalon has been promoting stimulants off-label. In September 2011, the U.S. Department of Justice subpoenaed Cephalon for documents related to its promotion of Nuvigil® and Provigil®. It is not the first time that the company has been allegedly in violation of promotional regulations. In 2008, the company pled guilty to Department of Justice charges of off-label marketing for Provigil® and two other drugs, paying $425 million to reimburse federal and state drug programs. It also paid $6.1 million to settle unfair trade charges from the Connecticut Attorney General. As part of the federal agreement, Cephalon, which is now owned by Teva, signed a corporate integrity agreement (CIA) with the Department of Justice that ends in 2013. It requires that the company review all sales representative plans for customer visits at least annually to ensure that all products are promoted "in a manner that complies with all applicable Federal health care program and FDA requirements."[12]

Dangers of Wakefulness

The off-label use of stimulants to promote everyday wakefulness and concentration in people without underlying medical conditions is not a benign problem.

Methylphenidate and amphetamines are associated with cardiovascular risks, sudden cardiac death, anxiety, restlessness, hypertension, tachycardia, and psychiatric

Diversion: By the Numbers

In one analysis of privately insured individuals with ADHD ages 18 to 49, an estimated 16.6 percent diverted their medication.[1] Other studies found that up to 26 percent of college students prescribed methylphenidate gave away or sold their medication.[3]

effects, all of which can increase physician office visits and long-term medical complications.[13] Stimulants can also be addictive, with 343,000 people ages 12 and older being treated for stimulant abuse or addiction in 2010.[14]

An analysis of calls to the American Association of Poison Control Centers' National Poison Data System between 1998 and 2005 found that calls related to ADHD medication abuse in teenagers rose substantially more than those for all other substance abuse victims. This increased evidence of stimulant abuse occurred even as the number of methylphenidate prescriptions fell.[15] As the authors noted: "The sharp increase, out of proportion to other poison center calls, suggests a rising problem with teen ADHD stimulant medication abuse."[15]

The side-effect profile of Nuvigil® and Provigil® are generally more favorable than those of ADHD stimulants, with two significant exceptions: an increased risk of serious rash, including Stevens-Johnson syndrome, and a growing concern about their addictive potential. When the drugs first came on the market, articles noted that it was not clear how, exactly, they worked, but highlighted their reduced potential for addiction compared to older stimulants. Recent human and animal studies, however, found that they bind to the same site on dopamine receptors as cocaine, raising concerns about their addiction potential.[16-17]

A 2004 article in the *New York Times* noted another concern: that as people mask their fatigue with medication, disorders like diabetes and sleep apnea could go undiagnosed, leading to significant comorbidities.[9] It is a valid concern given research that links sleep deprivation to a variety of health-related issues, including hypertension, impaired glucose regulation, obesity, and cardiovascular and cancer-related morbidity and mortality.[18-22]

Managing the Risk

"We recognized the potential of abuse issues around Provigil® when it first came out," said Lynn Nishida, RPh, Director of Pharmacy Services for RegenceRx, a pharmacy benefit manager based in Portland, Oregon. "It got this claim of fame as a lifestyle modification drug if you were falling asleep on the job or had shift-work disorder." It was soon also being touted for jet lag (note: the U.S. Food and Drug Administration denied a request from Cephalon to add a jet lag indication to Nuvigil® labeling). From the start, Nishida said, RegenceRx implemented formulary controls to make sure the stimulants were used only for a narcolepsy diagnosis. Other health plans have followed suit.

Tufts Health Plan has step-therapy requirements in place for Provigil®, requiring that patients first use amphetamines or methylphenidate for excessive sleepiness. It does not cover Provigil®, and notes that coverage is not approved for shift-work sleep disorder, generalized fatigue, jet lag, or sleep deprivation.[23]

HealthPartners requires prior authorization for Nuvigil®, allowing its use only for narcolepsy or idiopathic hypersomnolence objectively documented by a sleep lab study; extreme daytime sleepiness due to sleep apnea not resolved with CPAP; and MS-related fatigue (an off-label use) only after trying and failing amantadine. The formulary preference is for Nuvigil® over Provigil® given the increased cost of the latter (about $300 per month versus $900 for Provigil®), although that will likely change once generic modafinil is available this spring.[24]

With the newly developed adolescent treatment guidelines, RegenceRx's Nishida said the company is not planning any additional regulations around the ADHD stimulants, relying instead on existing policies such as maximum allowable daily limits and retrospective claim review to identify potential abuser patterns, including too many refills, vacation overrides, and filling the prescriptions at multiple pharmacies.

Looking Forward

The issue of prescription drug misuse in the U.S. has grown significantly in the past 10 years. But while opioid abuse tends to garner the greatest attention, health plans are also seeing increasing misuse of stimulants—both older drugs used to treat ADHD, and newer medications designed to address underlying sleep-related disorders. All stimulants carry a potential for addiction, and all have significant side effects that could lead to morbidities or even mortality. In addition, if patients who are prescribed stimulant medication divert their prescription, their condition may worsen, which in turn could lead to increased medical costs. Therefore, it is crucial that health plans address the potential for stimulant misuse—whether diversion or off-label use—through appropriate formulary controls and extensive network education for both patients and providers.

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Telemedicine: Changing the Landscape of Healthcare Delivery

In 2007, healthcare costs represented $2.1 trillion of the United States' gross domestic product, and this expenditure is expected to increase by nearly 20 percent within the next decade.[1] With healthcare expenses skyrocketing to record highs, managed care organizations are continually challenged to develop alternative healthcare management strategies that have the potential to improve quality while simultaneously minimizing overall costs. Many industry leaders believe that the transition to a more sustainable healthcare delivery system can be greatly assisted by the adoption of telemedicine applications. Telemedicine is the use of medical information that is exchanged from one site to another via electronic communications in order to improve patients' health status.[2]

Although the concept of telemedicine has been around for decades, its utilization has started increasing drastically in recent years. With 20 percent of Americans living in places where primary care physicians are scarce,[3] large health plans are beginning to appreciate the clinical and financial applications of telemedicine. Large insurance companies, such as UnitedHealth Group and several Blue Cross plans, have started marketing their telemedicine services. The organizations that are particularly interested in these services are the major employer groups. Additionally, the Centers for Medicare & Medicaid Services (CMS) are now reimbursing doctors and hospitals for providing remote care to rural and underserved areas.[4]

Services and Benefits

To develop a clinically and financially sustainable healthcare delivery system, innovative and cost-effective solutions need to be pursued. As outlined in Table 1, telemedicine offers a variety of clinical services that, if implemented correctly, can assist health plans in enhancing the quality of care provided to their patients and limiting unnecessary healthcare utilization. Many of these services are ideal for patients suffering from chronic and debilitating medical conditions whose mobility may be compromised by their disease state. Additionally, these are often the patients consuming a large portion of healthcare resources.

Telemedicine can also be a useful tool to satisfy certain federal regulations imposed on health plans. CMS requires that health plans covering Medicare Part

Table 1

Telemedicine Services[2]

- **Specialist referral services** typically involve a specialist assisting a general practitioner in rendering a diagnosis. This interaction may involve a live, remote consult, or the transmission of diagnostic images with a detailed patient history for a specialist to review at a later time.
- **Patient consultations** can involve using telecommunications to provide medical data, which may include audio and/or images, between a patient and a healthcare professional for use in rendering a diagnosis and treatment plan.
- **Remote patient monitoring** uses devices to remotely collect and send data to a monitoring station for interpretation. This may include monitoring vital signs, blood glucose, or electrocardiograms.
- **Medical education** provides continuing medical education credits for health professionals and special medical education seminars for targeted groups in remote locations.
- **Consumer medical and health information** includes the use of the Internet for consumers to obtain specialized health information and online discussion groups to provide peer-to-peer support.

D lives provide Medication Therapy Management (MTM) services to these patients. These programs must be designed to target beneficiaries who have multiple chronic conditions, are taking several medications, and are predicted to incur a large amount of healthcare resources.[5] Telemedicine may be a cost-effective solution to meeting, and exceeding, these federal requirements.

In a study published in the *New England Journal of Medicine,* the use of a telephonic care-management intervention reduced overall healthcare costs by 3.6 percent. The study enrolled 174,120 subjects with preexisting health insurance coverage that they received through one of seven employers. The healthcare team performing the outreach was comprised of registered nurses, licensed vocational nurses, dietitians, respiratory therapists, and pharmacists. The primary goal of the outreach was to teach patients a variety of self-care techniques and to ensure that the patients had a firm understanding of their medication regimens. The healthcare team contacted patients following hospital discharge in order to review, explain, and reinforce discharge instructions, and to motivate patients to make behavioral changes. The primary outcomes that were analyzed in this study were cost of care and the use of hospital, emergency room, and outpatient services. The results of the study revealed an overall expenditure reduction of $7.96 per person per month and a 10.1 percent reduction in hospital admission rates.[6] This study demonstrates how a targeted telephone care-management program can successfully reduce medical costs and hospitalizations in an insured patient population.

The use of telemedicine also has the ability to improve patient satisfaction rates within the managed care industry. Currently, many health plans are struggling to find cost-effective methods to improve customer satisfaction rates within their organizations. With the results from the Consumer Assessment of Healthcare Provider and Systems (CAHPS) survey being incorporated into the CMS star ratings, patient perceptions related to the quality of care they receive now affect health plan reimbursement. A relatively simple telemedicine initiative, such as a pharmacist-provided telephonic MTM program, is one strategy to improve these perceptions, and potentially a plan's overall star rating, while concurrently reducing healthcare expenditure.

Economic Impact of Telemedicine

Within the managed care industry, achieving positive clinical outcomes is always the highest priority. However, these clinical outcomes must be obtained while maintaining a sustainable financial structure and affordable premiums for beneficiaries. By implementing a comprehensive telemedicine program, health plans now have an opportunity to generate a substantial amount of cost-savings. It has been estimated that, in a 25-year period, a national telemedicine infrastructure would save $927 billion in healthcare costs for seniors and people with

disabilities.[7] Additionally, telemedicine can provide the resources necessary for early disease prevention and help reduce the need for costly physician involvement.[8,9] These uses alone have the ability to generate enormous financial savings.

By utilizing telemedicine solely to minimize patient transfers, the healthcare industry has the potential to save a substantial amount of unnecessary expenditures.[10] These savings have been demonstrated by:

- A 38 percent reduction in transfers from one hospital emergency department (ED) to another ($537 million)
- A 79 percent cut in transfers to physician offices and a 42 percent reduction in transfers to ED from correctional facilities ($270.3 million)
- A 14 percent cut in transfers from nursing homes to ED ($327 million)
- A 68 percent cut in transfers from nursing homes to physician offices ($479 million)
- A 45 percent reduction in unnecessary or redundant tests ($3.61 billion)

After accounting for additional costs, the substantial reductions in patient transfers, and the associated unnecessary resource utilization, it was estimated that the U.S. healthcare system could save up to $4.28 billion annually.[10] This represents a major opportunity for health plans to manage the continually escalating healthcare expenditure and to reduce inappropriate resource utilization.

Conclusion

Developing innovative telemedicine solutions can promote clinical and financial opportunities at the local, state, and federal levels. These services can begin with a simple program, such as telephonic outreach, and expand as far as national electronic databases. Ultimately, the tools, services, and devices provided by telemedicine can assist health plans across the country in delivering the highest level of medical care possible, improving customer satisfaction, and helping contain the continually increasing healthcare costs that are being observed across the nation.

Table 2

Benefits of Telemedicine[11]

- **Manage chronic diseases effectively:** Chronic conditions require long-term treatment and the use of multiple specialists, both of which significantly increase costs. Telemedicine can provide advancements in coordinated care and can assist healthcare professionals with early detection and intervention.
- **Improve care of elderly, home-bound, and physically challenged patients:** Telemedicine can reduce the frequency of visits to physician offices and hospital emergency rooms, and can potentially lead to greater convenience and compliance for elderly and home-based patients.
- **Empower patients regarding their own health:** Telemedicine provides an opportunity for patients and caregivers to play a greater role in their own care by raising the responsibility level of patients to take their medicines and report basic health metrics to their physicians.
- **Improve competitiveness of U.S. industry by controlling healthcare costs:** Telemedicine can provide a tool for companies and insurers to better control and manage healthcare spending by enabling greater use of remote monitoring of a patient's condition in order to minimize the need for acute care intervention.
- **Improve community and population health:** Telemedicine permits an easier exchange of information between public health services about rare or unusual health conditions, assists in the epidemiologic measurement of chronic diseases within a population, and helps to address public health crises, such as pandemic flu.
- **Source of creative, innovative employment within healthcare sector:** Telemedicine has grown to become a $3.9 billion industry. This expansion has generated employment opportunities in many facets of healthcare, such as information technology. A recent study estimates that advancements in health information technology would create or retain 212,000 U.S. jobs every year.[12]
- **Address possible future shortages of healthcare professionals:** Telemedicine services can better utilize current staffing models, whether at a hospital, in a physician's office, or at home. The availability of telemedicine technologies and procedures can also alleviate potential shortages of healthcare professionals by enabling remote consultations.

Economic Savings Associated with Incorporating Telehealth Applications in the Treatment of CHF

According to the Center for Aging Services Technology, patients managing their congestive heart failure (CHF) through the utilization of telehealth devices can reduce their healthcare utilization (physician office visits, ED visits, and rehospitalization) by an average of 30 percent. This would translate to an economic savings of $442 billion in a 25-year period.[13,14]

Effect of Telehealth on the Projected Economic Cost of CHF from 2005 to 2030, in Billions[13,14]

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Clinical and Financial Considerations for Oral Anticoagulants

Mark Huetten, RPh, Chief Pharmacy Officer, Coalition for Advanced Pharmacy Services (CAPS)

In 2010, the estimated economic burden of strokes in the United States was $73.7 billion.[1] Because this number is only projected to increase, the implementation of stroke prevention is critically important to the reduction of healthcare costs. For patients with atrial fibrillation, who are five times more likely to suffer a stroke compared with patients in normal sinus rhythm,[2,3] initiating and continuing a stroke prevention regimen is essential to increasing their quality of life and reducing unnecessary healthcare utilization.

The standard for stroke prevention therapy currently relies on an adjusted-dose vitamin K antagonist, such as warfarin. Warfarin has demonstrated effectiveness when the patient's international normalized ratio (INR) is kept within the therapeutic range of 2.0 to 3.0. However, keeping patients in this therapeutic range can be challenging, and patient compliance is often problematic. Although warfarin is an effective therapy and is readily available with a favorable cost profile, there are significant disadvantages that increase the treatment cost burden. In addition, the primary risk associated with warfarin—major bleeding—has made some patients and physicians wary of the drug. In fact, it is estimated that less than 60 percent of patients who have been diagnosed with atrial fibrillation are currently taking warfarin.[4] This presents a major opportunity for new agents to emerge in the marketplace and challenge warfarin as the gold standard of stroke prevention therapy.

In the past 18 months, two new and novel anticoagulants, dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) and rivaroxaban (Xarelto®, Bayer HealthCare AG), have entered the U.S. market. These new agents may provide atrial fibrillation patients with a more convenient option to minimize their risk of stroke and may potentially increase medication compliance. In addition, both anticoagulants have greater pharmacodynamic predictability than warfarin, and do not require frequent blood draws to verify appropriate anticoagulation.[5] However, real-world data on safety events is still being collected, and the results could hinder the widespread acceptance of these new anticoagulants by both patients and providers.

RE-LY Trial

Dabigatran, an oral thrombin inhibitor, was compared to warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), a

Table 1 Select RE-LY Data[6]

	Dabigatran, 110 mg	Dabigatran, 150 mg	Warfarin
	(n=6,015)	(n=6,076)	(n=6,022)
	%/Yr	%/Yr	%/Yr
Stroke or SE	1.53	1.11	1.69
Ischemic or unspecified stroke	1.34	0.92	1.20
Hemorrhagic stroke	0.12	0.10	0.38
Intracranial bleeding	0.23	0.30	0.74
MI	0.72	0.74	0.53
Major bleeding	2.71	3.11	3.36
Life-threatening bleeding	1.22	1.45	1.80
GI bleeding	1.12	1.51	1.02

non-inferiority trial that enrolled 18,133 patients with atrial fibrillation. Two doses of dabigatran, 110 mg and 150 mg, given twice daily, were studied. Time in therapeutic range (TTR) for patients taking warfarin was 64 percent during the trial.[6]

The higher dose of dabigatran (150 mg) was statistically superior to warfarin (p-value < 0.001) in preventing stroke or systemic embolism (SE); the lower dose of dabigatran (110 mg) was non-inferior. Hemorrhagic strokes per year were lower in both dabigatran groups compared with those reported in the warfarin treatment group. Overall, dabigatran showed a better safety profile than warfarin. However, there were two notable safety events, myocardial infarction (MI) and major gastrointestinal (GI) bleeding, seen in dabigatran patients.[6]

Mark Huetten, RPh

Based on the RE-LY study, the U.S. Food and Drug Administration (FDA) approved the 150 mg dose of dabigatran in October 2010, but not the 110 mg dose. The agency did not find a significant clinical benefit for the lower dose of dabigatran in a subgroup analysis, which included the elderly, patients who had previous bleeding events, and those with renal impairment. However, the FDA did approve a 75 mg dose of the drug, which was not studied in the RE-LY trial, for use in patients with severe renal impairment.[7]

In November 2011, the European Medicines Agency reported 256 fatal bleeds in patients taking dabigatran.[8] Separately, the FDA revised the label for dabigatran, instructing physicians to assess a patient's renal function prior to prescribing the drug. The label revision also advised physicians to administer the 75 mg dose for patients on dronedarone (Multaq®, Sanofi Aventis) or systemic ketoconazole, and to avoid prescribing dabigatran to patients with severe renal dysfunction taking permeability-glycoprotein inhibitors.[9] In December 2011, the FDA began an investigation into the post-approval incidence of major bleeding.[10]

It is possible that the real-world experience with dabigatran will also demonstrate a higher incidence of MI than that shown in RE-LY. A meta-analysis of seven clinical studies (n=30,514) of dabigatran showed that patients taking dabigatran had an odds ratio of having an MI or acute coronary syndrome (ACS) of 1.33 compared with patients taking the control drug. However, it is unclear whether dabigatran itself is associated with a higher incidence of MI and ACS or whether warfarin has a protective effect against these events.[11]

ROCKET AF Trial

The Rivaroxaban Once Daily Oral Director Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) enrolled 14,264 patients with nonvalvular atrial fibrillation. Dosing for rivaroxaban was 20 mg daily. The median TTR for patients taking warfarin was 58 percent during the study period.[12]

Rivaroxaban achieved non-inferiority to warfarin in stroke and SE prevention. On a per-protocol basis, the event rate for stroke or SE in the rivaroxaban group was 1.7

Table 2

Select ROCKET AF Data[12]

	Rivaroxaban		Warfarin	
	No. of Patients	Event Rate*	No. of Patients	Event Rate*
Efficacy				
Stroke (ischemic or hemorrhagic) and SE				
Per protocol	6,958	1.7	7,004	2.2
Intention to treat	7,081	2.1	7,090	2.4
Safety				
Major and clinically relevant non-major bleeding	7,111	14.9	7,125	14.5
Fatal bleeding		0.2		0.5
Critical bleeding		0.8		1.2
Intracranial hemorrhage		0.5		0.7

*Per 100 patient years

percent per 100 patient years compared with 2.2 percent for patients taking warfarin. There were 81 patients in the rivaroxaban arm that discontinued treatment prior to the formal end of ROCKET AF. After discontinuation of rivaroxaban, the event rate for stroke or SE increased to 4.7 percent per 100 patient years for these patients.[12]

Although major bleeding rates were similar between the two groups, there were differences in the types of major bleeding. Rivaroxaban resulted in a greater frequency of decreased hemoglobin levels, major GI bleeding, and transfusions. However, it had fewer fatal bleeds and fewer bleeds at critical anatomical sites, as well as a lower incidence of intracranial hemorrhage (ICH).[9]

Based on data from ROCKET AF, the FDA approved rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation in November 2011. Included in the labeling is a warning that patients should not discontinue the drug without consulting a healthcare professional first, as discontinuation could increase their risk of stroke.

New Agents: Benefits and Drawbacks

Dabigatran and rivaroxaban may offer several advantages over warfarin. In clinical trials, the higher dose of dabigatran demonstrated superiority against warfarin in the prevention of stroke and SE, and rivaroxaban was shown to be non-inferior to warfarin. In these trials, both dabigatran and rivaroxaban had fewer instances of intracranial bleeding and ICH. Both have greater pharmacodynamic predictability than warfarin, and neither requires INR monitoring. Therefore, patients are not subject to frequent blood draws or dose adjustments. In addition, patients do not face dietary restrictions with either of these new anticoagulants. Dabigatran and rivaroxaban also have fewer drug-to-drug interactions than warfarin.[13]

In general, healthcare professionals are enthusiastic about having more anticoagulation options. "We've been waiting for an alternative to warfarin almost since the day it was approved," said Daniel Labovitz, MD, Director of the Stern Stroke Center at Montefiore Medical Center in the Bronx. "Warfarin has so many drug and food interactions, even a highly compliant patient can have very volatile INR levels."

However, there are several issues that need to be resolved with the new anticoagulants. First, it remains to be seen whether the new anticoagulants enhance patient compliance. Second, it is unclear what, if any, clinical impact could arise from not having regular monitoring of anticoagulation levels. Finally, more research may be needed to inform a revision in stroke protocols, particularly with regard to the administration of tissue plasminogen activator (tPA).

Compliance

Poor compliance is perhaps the most common cause of treatment failure, and is directly associated with negative health outcomes.[14] If patients on warfarin therapy are not compliant, their likelihood of developing an SE increases enormously and can lead to a higher rate of hospitalizations and, potentially, disability. The frequent blood tests and finger sticks associated with warfarin therapy are a major reason for non-compliance and the discontinuation of therapy.[15] In addition, many patients are fearful of warfarin's side effects, which could also affect their compliance.

Table 3

Anticoagulant Therapies: Advantages and Disadvantages[2,5,6,11,12]

	Advantages	Disadvantages
Pradaxa® (dabigatran)	No INR monitoring or frequent blood draws Superior stroke and SE prevention vs. warfarin Lower incidence of hemorrhagic stroke vs. warfarin Reduced costs associated with side effects Fast onset and offset of action (beneficial for surgery patients)	No antidote Major GI bleeding Dyspepsia is a common complaint. Higher MI events vs. warfarin Dosing restrictions for patients taking dronedarone or systemic ketoconazole Contraindicated for patients with severe renal dysfunction on permeability-glycoprotein inhibitors High medication cost Twice-daily dosing Short duration of action (clotting risk in poorly adherent patients)
Xarelto® (rivaroxaban)	Once-daily dosing No INR monitoring or frequent blood draws Fewer incidents of intracranial hemorrhage vs. warfarin Reversal by prothrombin complex concentrate	Limited real-world data Higher incidence of decreased hemoglobin levels vs. warfarin Greater frequency of transfusions vs. warfarin High medication cost
Warfarin	Proven efficacy Cost of medication Readily accessible antidote Long-acting (lower clot risk in poorly adherent patients) Once-daily dosing	Cost of monitoring INR Extensive drug/drug and drug/food interactions Slow offset of action Increased bleeding risk High discontinuation rates Need for bridge therapy when patients are taken off for a period of time (surgery)

The new anticoagulants, which have fewer lifestyle restrictions and may have more favorable safety profiles, may result in enhanced patient compliance. "Patients are very grateful to escape the frequent blood draws of warfarin," said Labovitz. "Pradaxa's been a real godsend in that way. Patients are willing to spend more for Pradaxa in order to avoid the inconvenience of warfarin. The management of warfarin is a real quality-of-life issue. It's not clear whether patients will be more or less compliant with Pradaxa, but they do seem happier with it."

Some healthcare practitioners worry about patient compliance, given the relatively short half-lives of dabigatran (12–17 hours) and rivaroxaban (5–9 hours). "Adherence is particularly important. If patients miss only a few doses of dabigatran, they will no longer be anticoagulated, and, if they double dose, they will be at a higher risk for bleeding," said Mark Rogers, PharmD, at The Westerly Hospital in Rhode Island.

Labovitz agrees that adherence is crucial. "The two leading causes of medication noncompliance are medication cost and dosing frequency. Pradaxa, which has to be taken twice a day, has both of those problems. I counsel my patients intensively on the need for strict compliance," Labovitz said. There could be fewer concerns related to patient compliance with rivaroxaban, which requires the patient to take a single daily dose at dinnertime.

Testing Therapeutic Levels

Lack of routine monitoring with the new anticoagulants may produce a modest degree of hesitancy among some physicians. However, other clinicians do not view this as a major concern. "Monthly monitoring doesn't tell you if a patient missed a couple of doses of warfarin over the course of a month. Because of that, I'm not bothered by the lack of monitoring for Pradaxa," Labovitz said. "If I'm concerned

that a patient isn't being compliant, I'll order a thrombin time test. Some people do experience bleeding, though, so I wouldn't call Pradaxa a home run yet."

Lack of Antidote and Stroke Protocols

A major concern related to dabigatran is its lack of antidote if a patient should have an accident or require an emergency interventional procedure. "You can't reverse Pradaxa," said Roberta Sposato, RPh, at The Westerly Hospital. "You can use a prothrombin antidote for Xarelto and get a partial reversal. You don't have that for Pradaxa." A small study of 12 healthy volunteers showed that a prothrombin complex concentrate (PCC) immediately reversed the anticoagulant effect of rivaroxaban, but not dabigatran. After taking dabigatran and then receiving PCC or saline solution, it took 24 hours for the volunteers' PTT to normalize.[16]

Because of this, dabigatran may negate the administration of tPA if a patient has an ischemic stroke. "You can approximate the anticoagulation effect, but there is no clear way, or standard of care, for monitoring the actual anticoagulation effect," Rogers said. Thus, neurologists may have reservations when prescribing tPA for patients taking dabigatran. Separately, clinical data demonstrating the reversal of rivaroxaban in patients with atrial fibrillation, not just healthy volunteers, may be needed before tPA protocols are revised to include rivaroxaban.

Cost Analysis

The new branded agents cost considerably more per unit than warfarin. However, when evaluating the cost-effectiveness of different medication therapies, the analysis must go beyond the initial cost of medication. The outcomes, side effects, and monitoring costs all contribute to the overall healthcare spend. Thus, cost containment strategies must strive to keep patients out of the hospital and functioning without assistance. Reducing the rates of preventable hospitalizations and disability is critical in the containment of unnecessary healthcare utilization.

	Unit Price (WAC)	Dosing Frequency	Total WAC/Day
Pradaxa®	$3.645	BID	$7.29
Xarelto®	$7.29	QD	$7.29

Note: The cost of warfarin is variable. The wholesale acquisition cost (WAC) of a Mylan-manufactured 100 ct bottle of 5 mg warfarin is $16.02.

Source: Price Rx

It is well established that the use of warfarin to prevent hospitalization and disability due to strokes reduces overall healthcare spend in patients with AF. However, warfarin is not without its disadvantages. Due to the narrow therapeutic window and drug/dietary interactions, patients receiving warfarin therapy require frequent monitoring and dosage adjustments to prohibit over- or under-coagulation. This monitoring consumes a significant amount of time and healthcare resources. The management of warfarin-related side effects also has the ability to increase healthcare costs. ICH and major bleeding are costly adverse effects of over-anticoagulation. This is an expense that cannot be ignored, as more than 3 percent of patients annually experience a major bleed.[6] With an estimated 1.5 million Americans on warfarin therapy,[17] these financial burdens can quickly accumulate. Though the benefits of warfarin lower the overall healthcare spend by reducing hospitalization and disability, there remains room for financial improvement.

Many experts believe that the new anticoagulants may be a solution to the clinical and financial limitations of warfarin therapy. In order to impact the current standard of care, the financial benefits of dabigatran and rivaroxaban must be assessed through three primary mechanisms: decreased monitoring costs, reduced expenses of side effects, and reduction of unnecessary hospitalizations and disability due to strokes. The current evidence evaluating the new anticoagulant therapies shows predictable pharmacokinetics. This eliminates the need for frequent INR monitoring and dose modification, which increase therapy costs and decrease patient satisfaction. Medication compliance and persistence also has the potential to increase with dabigatran and rivaroxaban, which could improve overall patient health outcomes and decrease healthcare utilization in the process.[14]

As previously discussed, the risk of patients developing a hemorrhagic stroke or intracranial bleeding was reduced in patients in the dabigatran treatment group in the RE-LY trial,[6] and patients in the rivaroxaban treatment group in the ROCKET AF trial experienced fewer fatal and critical bleeds and had a lower incidence of intracranial hemorrhage.[12] The reduction of these events, combined with the elimination of monitoring costs, may justify the use of these new agents over warfarin from both a clinical and a financial perspective.

Prior to the introduction of dabigatran in the U.S., James V. Freeman and colleagues performed a cost-effective analysis of dabigatran compared to warfarin based on data from the RE-LY trial. The analysis included estimates for rates of ischemic stroke, intracranial hemorrhage, stroke severity, MI risk, and costs for medication and routine monitoring. The analysis revealed an incremental cost-effectiveness ratio (ICER) of $45,372 per quality-adjusted life years (QALY) for dabigatran compared to warfarin, which is below the conventional benchmark of acceptable cost of $50,000 per QALY. Dabigatran's ICER reflected the higher per-unit cost of dabigatran and fewer ischemic and hemorrhagic strokes, but an increased number of MIs, compared to patients who received warfarin therapy. After analyzing the total cost of treatment, including medication, monitoring, and side effects, the authors concluded that dabigatran would be cost-effective at a price of less than $13.70 per day for the 150 mg twice-daily dosing schedule.[18]

Of note, dabigatran's actual wholesale acquisition cost (WAC), which reflects the list price for wholesalers, distributors, and other direct buyers before any available rebates or discounts, is $7.29 per day. This figure is significantly less than the estimated price used in Freeman's analysis, which suggests that dabigatran's true cost per QALY gained could be significantly lower than the benchmark of $50,000. However, the financial benefits of dabigatran could be somewhat offset by a higher incidence of MI than was demonstrated in the RE-LY trial and was assumed in Freeman's analysis. No cost-effective analysis has been published on rivaroxaban use in patients with atrial fibrillation.

Conclusion

The reduction of negative health outcomes is the key to determining the true cost-effectiveness of anticoagulant therapy. Due to the potential reduction in hospitalizations and disability for dabigatran and rivaroxaban, the cost of therapy may be beneficial despite the increased unit price over warfarin. Both dabigatran and rivaroxaban have higher or comparable efficacy to warfarin in preventing stroke and SE based on data from the RE-LY and ROCKET AF clinical trials. However, it remains to be seen whether this will translate into real-world experience. Recent reports on dabigatran have cast some doubts on its presumed better safety profile, and it is possible that safety events not seen in either RE-LY or ROCKET AF will come to light.

In addition, it is important to realize that cost-effectiveness evaluation is strictly theoretical, and it may not apply to every organization. Costs must be weighed on an individual health plan basis, as the contracted pricing and the health plan's cost-sharing structure also affect whether the new anticoagulant therapies will be beneficial from a financial perspective.

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Please see brief summary of Prescribing Information on adjacent page.

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PRECAUTIONS: General: Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal. LEVEMIR® is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration. **LEVEMIR® should not be diluted or mixed with any other insulin preparations** (see PRECAUTIONS, Mixing of Insulins). Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins. As with all insulin preparations, the time course of LEVEMIR® action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity. Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. **Hypoglycemia:** As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR®. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia. The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR®, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia. **Renal Impairment:** As with other insulins, the requirements for LEVEMIR® may need to be adjusted in patients with renal impairment. **Hepatic Impairment:** As with other insulins, the requirements for LEVEMIR® may need to be adjusted in patients with hepatic impairment. **Injection Site and Allergic Reactions:** As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR®. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. *Systemic allergy:* Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening. **Intercurrent Conditions:** Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses. **Information for Patients:** LEVEMIR® must only be used if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of LEVEMIR® therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR® "Patient Information" circular for additional information. As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia. Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy). **Laboratory Tests:** As with all insulin therapy, the therapeutic response to LEVEMIR® should be monitored by periodic blood glucose tests. Periodic measurement of HbA_{1c} is recommended for the monitoring of long-term glycemic control. **Drug Interactions:** A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives). The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics. Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent. The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs. **Mixing of Insulins:** If LEVEMIR® is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR® with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in $AUC_{(0-2h)}$ and C_{max} for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR® was less than 50%. **LEVEMIR® should NOT be mixed or diluted with any other insulin preparations. Carcinogenicity, Mutagenicity, Impairment of Fertility:** Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test. **Pregnancy: Teratogenic Effects: Pregnancy Category C:** In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity. **Nursing mothers:** It is unknown whether LEVEMIR® is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR® is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both. **Pediatric use:** In a controlled clinical study, HbA_{1c} concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR® and patients treated with NPH human insulin. **Geriatric use:** Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR®, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

ADVERSE REACTIONS: Adverse events commonly associated with human insulin therapy include the following: **Body as Whole:** allergic reactions (see PRECAUTIONS, Allergy). **Skin and Appendages:** lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR® than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy). **Other: Hypoglycemia:** (see WARNINGS and PRECAUTIONS). In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR® was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4). **Weight gain:** In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR® was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR® and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

Table 4: Safety Information on Clinical Studies*

			Weight (kg)		Hypoglycemia (events/subject/month)	
	Treatment	# of subjects	Baseline	End of treatment	Major**	Minor***
Type 1						
Study A	LEVEMIR®	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR®	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D Pediatric	LEVEMIR®	N=232	N/A	N/A	0.076	2.677
	NPH	N=115	N/A	N/A	0.083	3.203
Type 2						
Study E	LEVEMIR®	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR®	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

* See CLINICAL STUDIES section for description of individual studies
** Major = requires assistance of another individual because of neurologic impairment
*** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

More detailed information is available upon request.

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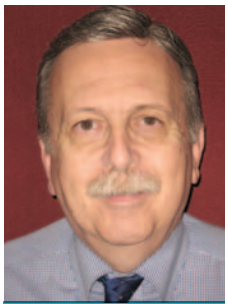
Healthcare Reform: Transitioning to Accountable Care

William J. Cardarelli, PharmD, Director of Pharmacy Revenue and Supply, Atrius Health, Harvard and Vanguard Medical Associates; and Christine Welniak

Total Medicare spending comprised 20 percent of all national healthcare expenditures in 2010.[1] Accountable Care Organizations (ACOs) are considered one way to control Medicare costs in anticipation of the aging baby boomer population, the first of whom became Medicare eligible in 2011. In response to the anticipated increase in Medicare patients, the federal government is striving to find affordable solutions to provide all Medicare beneficiaries with the highest quality of care possible. In response to this and as a method to broaden the appeal of ACOs, the Centers for Medicare & Medicaid Services (CMS) relaxed the initial requirements for ACOs in the fall of 2011.

The final ACO rule gives healthcare providers the option to choose a one-sided track (i.e., share in savings, but not losses), stipulated 33 quality metrics (down from 65 in the proposed rule; see Table 1), and removed the requirement for electronic health records (EHRs).[2] Separately, physician practices with less than $50 million in revenue, as well as small rural hospitals, are now eligible for CMS' Advanced Payment Model, which would help defray some of the initial upfront capital investment necessary for transitioning to an ACO.[3]

Despite the easing of requirements and the Advanced Payment Model, most observers believe that the upfront financial investment remains substantial. Quantifying an average capital outlay is difficult, as it varies based on an organization's existing infrastructure, size, and goals. Therefore, the cost of transitioning to an ACO model may make the most economic sense to providers in geographic areas with a large population of current or soon-to-be Medicare beneficiaries. Providers who predominantly serve a younger population may not be able to recoup their initial investment from shared savings with Medicare.



William J. Cardarelli, PharmD

Theory Put into Practice

ACOs mark a change in the way that healthcare is delivered. The ACO model necessitates a cultural change within provider organizations, wherein all personnel have a responsibility to eliminate costs that do not contribute to delivering quality care to the patient. This, combined with a healthcare delivery model predicated on the primary care physician (PCP) appropriately coordinating care, will improve patient outcomes and lower healthcare expenditures—at least in theory.

Table 1

ACO Quality-of-Care Performance Measures[4]

Domain	Performance Measure
Patient experience (CAHPS)	1. Getting timely care, appointments, and information* 2. How well your doctors communicate* 3. Patients' rating of doctor* 4. Access to specialists* 5. Health promotion and education* 6. Shared decision making* 7. Health status/functional status
Care coordination/ patient safety	8. Risk-standardized, all condition readmissions 9. Ambulatory sensitive conditions admissions: Chronic obstructive pulmonary disease* 10. Ambulatory sensitive conditions admissions: Congestive heart failure* 11. Percent of PCPs who successfully qualify for an EHR incentive program payment* 12. Medication reconciliation: Reconciliation after discharge from an inpatient facility* 13. Falls: Screening for fall risk*
Preventive health	14. Influenza immunization* 15. Pneumococcal vaccination* 16. Adult weight screening and follow up* 17. Tobacco use assessment and tobacco cessation intervention* 18. Depression screening* 19. Colorectal cancer screening 20. Mammography screening 21. Proportion of adults 18+ who had their blood pressure measured within the preceding two years
At-risk population	22. Diabetes composite (all or nothing scoring): HbA_{1c} control (<8 percent)* 23. Diabetes composite (all or nothing scoring): Low-density lipoprotein (<100)* 24. Diabetes composite (all or nothing scoring): Blood pressure (<140/90)* 25. Diabetes composite (all or nothing scoring): Tobacco non-use* 26. Diabetes composite (all or nothing scoring): Aspirin use* 27. Diabetes mellitus: HbA_{1c} poor control (>9 percent)* 28. Hypertension: Blood pressure control* 29. Ischemic Vascular Disease: Complete lipid profile and LDL control (<100 mg/dl)* 30. Ischemic Vascular Disease: Use of aspirin or another antithrombotic* 31. Heart Failure: Beta-blocker therapy for left ventricular systolic dysfunction 32. Coronary artery disease composite (all or nothing scoring): Drug therapy for lowering LDL cholesterol 33. Coronary artery disease composite (all or nothing scoring): Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy for patients with coronary artery disease and diabetes and/or left ventricular systolic dysfunction

*ACOs will be rewarded based on these 25 performance measures beginning in 2013. Performance for all measures will start in 2014.

Critics of ACOs claim that this approach is simply a thinly disguised return to the capitated gatekeeper model that proved so unsuccessful in the early 1990s. In that model, the PCP rigidly controlled patient movement through the continuum of care. While the funding contains some similarities, an important difference in the ACO approach is that patients have total freedom to use physicians and facilities.

This patient empowerment will force PCPs to be more accessible and to develop strategies to motivate patients to access care within that physician's network. Specialists will not only be expected to provide excellent clinical care, but also to contribute to an improved patient experience.

Whether quality of care is actually improved and substantial savings can be achieved will remain unknown for several years, as the ACO program only became effective on January 3, 2012. ACOs will report data on quality measures this year, and CMS plans to set benchmarks on these performance measures in early 2013. ACOs will need to demonstrate their performance on 25 metrics in 2013 and on all 33 metrics in 2014 in order to participate in any financial savings.[4]

In addition to meeting or exceeding quality metrics, ACOs must achieve a minimum savings rate (MSR) that will be compared against a benchmark of Medicare expenditures. The MSR for ACOs that have opted not to share potential losses (Track 1) ranges from 2 percent to 3.9 percent, depending on the size of the ACO's patient population. The

> **"In essence, an ACO embodies the idea of enforced internal efficiencies."**
>
> *– Joseph Fortuna, MD, Chairman of the healthcare division of ASQ*

MSR for ACOs willing to share losses with Medicare (Track 2) is set at 2 percent.[5]

Blue Cross Blue Shield of Massachusetts (BCBSMA) has demonstrated that such a level of savings is achievable. BCBSMA's Alternative Quality Contract (AQC), a global payment system implemented in 2009, provides bonuses to physicians based on cost and quality metrics. Quarterly healthcare expenditures per AQC patient were $808 in 2009, versus $854 for patients in the control group. Although healthcare spending increased for both groups, it was almost 15 percentage points lower for AQC patients. After accounting for infrastructure investment and bonuses, the AQC group recorded a 1.9 percent savings compared to the control group. AQC groups had average budget surpluses of 3 percent for the year. Resource utilization did not differ considerably between the groups. Rather, AQC's better control of healthcare costs primarily reflected a change in patient referrals (e.g., sending patients to providers who charge lower fees).[6]

Potential Financial Rewards

If quality standards and target MSRs are met, Track 1 ACOs will be rewarded with up to 50 percent of the savings. Track 2 ACOs can earn up to 60 percent of the savings.[7] However, it remains unclear how these percentages will translate to actual dollars. Depending on the amount of reimbursement, it may not be enough to offset the initial investment needed to transition to an ACO model.

Looking at initiatives previously implemented at ACO-like entities can provide a glimpse into the potential savings that can be achieved. Intermountain Healthcare, an integrated healthcare system with approximately 160 clinics and 23 hospitals in Utah and Idaho, was an early adopter of applying a "lean" methodology to the practice of medicine. This strategy is used in manufacturing industries to achieve efficiencies and eliminate waste.

Specifically, Intermountain sought to identify variances in clinical processes and determine protocols to reduce costs without sacrificing patient care. In one early analysis, Intermountain Healthcare found that 11 percent of its healthcare expenses were for pregnancy, labor, and delivery. Intermountain evaluated the clinical processes and gauged the variable expenses, finding that 28 percent of pregnancy inductions did not meet the criteria for clinical appropriateness. Intermountain now has a protocol for elective induction of pregnancies. If the patient does not meet certain criteria, elective induction can only occur if the chair of obstetrics or a perinatologist approves the procedure.[8]

Following the implementation of this protocol, the number of elective inductions that were not deemed clinically necessary fell to less than 2 percent of all inductions. The protocol also resulted in fewer unplanned cesarean deliveries. Intermountain estimates that this single protocol resulted in an annual cost-savings of approximately $41 million.[8]

Virginia Mason Medical Center, which has one acute care hospital and about 450 salaried physicians in Seattle, adopted a lean methodology in 1999, after recording two years of losses. It embarked on a process of defining quality and better care. At Virginia Mason, better care meant standardizing processes based on medical evidence and providing an "impeccable" patient experience.[9]

Headache is one area in which Virginia Mason applied the lean methodology. The Medical Center found that 80 percent of its patients with uncomplicated headaches did not require magnetic resonance imaging (MRI). Chart review, however, showed that a large percentage of patients with uncomplicated headaches underwent MRI. As a result, Virginia Mason developed a telephone protocol for nonmedical personnel who could triage and refer patients based on responses to a questionnaire. Following implementation of this protocol, MRI scans for uncomplicated headaches decreased 23.2 percent.[9]

Although specific cost-savings in dollars have not yet

been calculated, Virginia Mason believes that the reduction in MRI costs, as well as in patient referrals to nurse practitioners instead of specialists or PCPs, has dramatically reduced the costs associated with caring for patients with uncomplicated headaches.[9]

Characteristics of an ACO

For providers considering a transition to the ACO model, detailed planning and the ability to communicate a unified message to all stakeholders are essential. Other key characteristics include:

- **Patient-centered approach.** With seven of the 33 performance metrics tied to a patient's perception of the quality of care he or she receives, an ACO's activities must be planned, implemented, and assessed with the patient in mind. In fact, Christine Leyden, RN, Senior Vice President of Client Services at URAC, a healthcare accreditation and education organization, recommends having patients involved in the planning stages. As new initiatives and processes are implemented, continued engagement and communication with patients is essential. For instance, as providers begin to use unfamiliar systems, office efficiency may temporarily drop. This, in turn, could impact how an ACO performs on CMS' first quality measure—how patients rate their ability to get timely care, appointments, and information. In addition, CMS' quality measures also include patients' assessments of an ACO's health promotion and education, which means that providers need to evaluate, and perhaps bolster, the resources available for patient education and support.
- **Team-oriented culture.** A continuum of care and a multidisciplinary approach, rather than the treatment of patients as discrete episodes, is integral to the ACO model. Although Medicare beneficiaries are attributed to a PCP, the ACO model differs from that of managed care, where the PCP was the gatekeeper. Instead, in the ACO model, a PCP is more akin to a healthcare coach or advocate. In addition, other healthcare and administrative personnel have an elevated role in the ACO model, which depends on robust communication, data integration, patient experience, and cost reduction. It is often assumed that negative physician attitudes about a team-oriented culture will create a barrier to the adoption of ACOs, or will limit the ability to achieve savings. While that remains a possibility, physician reluctance can often be circumvented by clear communication of goals by the ACO's leadership.
- **"Lean" methodology.** Although reduction in duplicative or unnecessary tests is an oft-cited example of how ACOs can control healthcare expenditures, healthcare providers must go further in order to realize cost-savings. Because of this, ACOs might be well served by applying a lean methodology to healthcare delivery. Lean methodologies are used by manufacturers to streamline processes, create efficiencies, and eliminate waste. When applied to medicine, this equates to clinical protocols within discrete settings, (e.g., physician's offices, hospitals, and post-acute care facilities), as well as protocols for discharge care and follow-up visits. "In essence, an ACO embodies the idea of enforced internal efficiencies," said Joseph Fortuna, MD, Chairman of the healthcare division of ASQ, a global forum on quality and processes. By adhering to such protocols, hospital re-admissions could be reduced, creating a large cost-savings. While providers clearly have an incentive to reduce hospital re-admissions in order to avoid penalties, substantial savings can be achieved in specific hospital departments or office settings through thoughtful clinical protocols. As noted previously, Intermountain Healthcare was able to achieve an estimated $41 million in annual savings based on changing a single protocol in the obstetrics department, while Virginia Mason Medical Center was able to reduce the use of MRI for patients with uncomplicated headaches by 23 percent. Under a lean methodology, all employees, not just physicians and administrators, are charged with reducing waste. "Everyone in an ACO has to be a waste buster," said Dr. Fortuna.
- **Sophisticated information technology infrastructure.** Data collection is at the heart of the ACO model. Systems must be in place to coordinate care, record and monitor outcomes, and track healthcare costs. Much attention has been placed on EHRs, but these are just one part of the necessary information technology infrastructure. Interoperable systems that permit secure transmission of data between physician offices, hospitals, and medical homes, among others, are required. Systems and processes that support the dissemination of protocols for treatment of care are needed. In addition, ACOs must be able to monitor referral patterns and identify trends in healthcare resource utilization. They also

continued

must have systems that accurately pinpoint accountability and assist in the allocation of shared savings. Finally, although CMS removed the EHR requirement from the final ACO ruling, EHRs may be instrumental in achieving performance measurements and cost-savings. EHRs can quickly inform the PCP of items to address with a patient during an office visit, whether they are glucose or LDL levels. This prioritization of a patient's medical condition and history could help avoid costly hospitalizations or emergency room visits for patients with multiple chronic diseases. EHRs also foster more meaningful physician and patient interactions, which could positively affect the CMS performance measures based on patient satisfaction.

■ **Self-evaluation.** Continued self-study is embedded in lean methodologies. In fact, it may be best to view ACOs as organizations in which clinical processes continue to evolve. Even after resources have been dedicated to analyzing clinical decisions juxtaposed against costs, the first attempts to streamline processes and to improve patient care may not be effective. Intermountain had two failed attempts at reducing costs in its obstetrics department before it arrived at its protocol for the elective induction of pregnancy. Multidisciplinary teams at an ACO must measure and assess each new process to determine whether it meets the ACO's criteria for effectiveness. If not, self-evaluation could identify key data or metrics that could better inform the clinical process.

Looking Ahead

Traditional fee-for-service spending by Medicare increased 5 percent in 2010; this exceeded private payor spending, which increased by 2.4 percent.[1] Of note, these numbers reflect healthcare spending in the year before the first baby boomers reached the age of 65. By 2020, the number of individuals aged 65 or older is expected to increase by 36 percent to 54.8 million Americans, up from 40.2 million in 2010.[10]

Clearly, managing costs and chronic conditions will become more important over the next several years. The nascent ACO program is one attempt to reduce costs without sacrificing patient care, and could result in a set of best practices that could be disseminated nationally. However, whether the ACO model is broadly adopted throughout the United States may depend as much on the 2012 political elections as it does on the ACOs' ability to prove viable. The current ACO requirements were developed as part of the Obama administration's healthcare reform legislation. As healthcare reform is always a major topic of political debate, the regulatory decisions made under the current presidential administration will likely receive a substantial amount of scrutiny as the 2012 presidential election draws near. If Republicans take control of the Senate and White House following the upcoming election, it is likely that they would move to repeal President Obama's healthcare plan, which, if successful, would ultimately render current ACOs ineffective and obsolete.

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Pioneer ACOs

The Center for Medicare & Medicaid Innovation has selected 32 providers to be part of its Pioneer ACO program. Most of the selected providers already have experience coordinating care between PCPs, hospitals, and post-acute care facilities. Pioneer ACOs will assume a higher level of risk in terms of the amount of losses they are committed to share with Medicare, compared with ACOs that are not part of the program. If Pioneer ACOs achieve a certain level of savings in the first two years of the program, reimbursement will be transitioned to a population-based model. This reimbursement schema has yet to be finalized.

Pioneer ACOs include:

Organization	Service Area
Allina Hospitals & Clinics	Minnesota and western Wisconsin
Atrius Health	Eastern and central Massachusetts
Banner Health Network	Phoenix metropolitan area
Bellin-Thedacare Healthcare Partners	Northeast Wisconsin
Beth Israel Deaconess Physician Organization	Eastern Massachusetts
Bronx Accountable Healthcare Network (BAHN)	New York City (the Bronx) and lower Westchester County, NY
Brown & Toland Physicians	San Francisco Bay Area
Dartmouth-Hitchcock ACO	New Hampshire and eastern Vermont
Eastern Maine Healthcare System	Central, eastern, and northern Maine
Fairview Health Systems	Minneapolis metropolitan area
Franciscan Alliance	Indianapolis and central Indiana
Genesys PHO	Southeastern Michigan
Healthcare Partners Medical Group	Los Angeles and Orange counties
Healthcare Partners of Nevada	Clark and Nye counties, Nevada
Heritage California ACO	Southern, central, and coastal California
JSA Medical Group, a division of HealthCare Partners	Orlando, Tampa Bay, and surrounding areas in southern Florida
Michigan Pioneer ACO	Southeastern Michigan
Monarch Healthcare	Orange County, California
Mount Auburn Cambridge Independent Practice Association (MACIPA)	Eastern Massachusetts
North Texas ACO	Tarrant, Johnson, and Parker counties, Texas
OSF Healthcare System	Central Illinois
Park Nicollet Health Services	Minneapolis metropolitan area
Partners Healthcare	Eastern Massachusetts
Physician Health Partners	Denver metropolitan area
Presbyterian Healthcare Services-Central New Mexico Pioneer Accountable Care Organization	Central New Mexico
Primecare Medical Network	San Bernardino and Riverside counties, California
Renaissance Medical Management Company	Southeastern Pennsylvania
Seton Health Alliance	Central Texas
Sharp Healthcare System	San Diego County
Steward Health Care System	Eastern Massachusetts
TriHealth, Inc.	Northwest Central Iowa
University of Michigan	Southeastern Michigan

Source: Center for Medicare & Medicaid Innovation

PIPELINE TRENDS

NEW DRUG APPROVALS

EPILEPSY

Onfi™ (clobazam)
Approved: December 14, 2011
Formulation: Tablet
Manufacturer: Lundbeck
Indication: Onfi™ (clobazam) is a benzodiazepine approved for the treatment of patients with Lennox-Gastaut syndrome.

OPHTHALMOLOGY

Zioptan™ (tafluprost)
Approved: February 10, 2012
Formulation: Ophthalmic solution
Manufacturer: Merck Sharp & Dohme Corp.
Indication: Zioptan™ (tafluprost) is a prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

TOXICOLOGY

Voraxaze® (glucarpidase)
Approved: January 17, 2012
Formulation: Injection
Manufacturer: BTG International
Indication: Voraxaze® (glucarpidase) is an enzyme approved to treat toxic plasma methotrexate levels in patients with delayed methotrexate clearance due to impaired renal function.

NEW FDA-APPROVED INDICATIONS

Drug Name	Approved	New Indication
Byetta® (exenatide)	October 19, 2011	Approved for use in conjunction with insulin glargine
Cialis® (tadalafil)	October 7, 2011	Once-daily treatment for benign prostatic hyperplasia (BPH)
Keppra® (levetiracetam)	December 16, 2011	Treatment age expanded to include infants and children from 1 month of age with partial onset seizures
Xarelto® (rivaroxaban)	November 4, 2011	Stroke prevention in patients with atrial fibrillation
Vyvanse® (lisdexamfetamine dismesylate)	January 31, 2012	Maintenance treatment in adults with Attention Deficit Hyperactivity Disorder (ADHD)

Upcoming PDUFA Dates

Generic Name	Trade Name	Manufacturer	Indication	PDUFA Date
Phentermine and Topiramate	Qnexa	VIVUS, Inc.	Obesity	April 17, 2012
Alogliptin and Alogliptin/Pioglitazone	Nesina	Takeda Pharmaceutical Company Limited	Type 2 Diabetes Mellitus (T2DM)	April 25, 2012
Methylnaltrexone	Relistor	Salix Pharmaceuticals, Inc.	Opioid-induced constipation (OIC) in patients with non-cancer pain	April 27, 2012
Staccato Loxapine	Adasuve	Alexza Pharmaceuticals, Inc.	Schizophrenia or bipolar disorder	May 4, 2012

Lipitor Generic: Competitive Pricing Expected Due to Multiple Generics in Near Future

On November 30, 2011, Ranbaxy Laboratories released the first generic formulation of Lipitor. Its launch came with great anticipation as the company has gone through extensive patent litigations with Pfizer prior to its launch and branded Lipitor is responsible for nearly $8 billion in U.S. sales annually. Ranbaxy has the 180-day semi-exclusivity rights to market the first Lipitor generic, since it was the first manufacturer to challenge Pfizer's patents. On the same day, Watson released its authorized generic, which is produced by Pfizer, but packaged and distributed by Watson. Price erosion is expected due to the known competition Ranbaxy will face post-exclusivity (as early as June 2012); however, it is too early to predict the extent. Dr. Reddy's Laboratories is one of the known companies that will be launching a Lipitor generic once the exclusivity period expires. For now, Dr. Reddy's is spending those 180 days strategizing the release of its Lipitor generic formulation and focusing on how to approach the market.

Disclosures: The information contained in Pipeline Trends is current as of February 2012. Estimated dates are subject to change according to additional indication/approvals, patents, patent litigation, etc. Information available from **www.fda.gov.**

NEW FORMULATIONS AND DOSAGE FORMS

Drug Name	Manufacturer	Approved	Advertised Advantage
Anturol® (oxybutynin) 3% gel	Antares Pharma	December 7, 2011	New transdermal oxybutynin gel strength for the treatment of overactive bladder. Due to the transdermal route of administration, the first-pass effect is avoided, thus decreasing incidence of adverse effects, such as dry mouth and constipation.
Bydureon™ (exenatide) extended-release injectable suspension	Amylin Pharmaceuticals	January 27, 2012	A once-weekly formulation of exenatide indicated as an adjunct therapy to diet and exercise to improve glycemic control in patients with T2DM
Combivent® Respimat® (ipratropium bromide and albuterol sulfate) inhalation spray	Boehringer Ingelheim	October 11, 2011	Slow-moving mist (rather than a propellant-based delivery system) indicated for the treatment of COPD
Edarbyclor™ (azilsartan medoxomil/ chlorthalidone) tablet	Takeda Pharmaceutical Company Limited	December 20, 2011	A novel angiotensin receptor blocker (ARB) and diuretic combination approved for the treatment of hypertension
Forfivo™ XL (bupropion HCl) extended-release tablet	IntelGenx Corp.	November 10, 2011	A new high-strength (450 mg) formulation of bupropion HCl extended-release approved for the treatment of major depressive disorder
Giazo™ (balsalazide disodium) tablet	Salix Pharmaceuticals, Inc.	February 3, 2012	A locally acting aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older
Intermezzo® (zolpidem tartrate) sublingual tablet (C-IV)	Transcept Pharmaceuticals, Inc.	November 23, 2011	Approved for PRN use to treat insomnia characterized by middle-of-the-night waking followed by difficulty returning to sleep
Janumet® XR (sitagliptin/metformin HCl) extended-release tablet	Merck Sharp & Dohme Corp.	February 2, 2012	A once-daily formulation indicated to improve glycemic control in patients with T2DM and may also enhance medication adherence
Jentadueto® (linagliptin/ metforming HCl) tablet	Boehringer Ingelheim	January 30, 2012	A combination product of linagliptin and metformin indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM
Juvisync® (sitagliptin/ simvastatin) tablet	Merck Sharp & Dohme Corp.	October 10, 2011	A once-daily combination of simvastatin and sitagliptin that has the potential to decrease pill burden
Subsys® (fentanyl) sublingual spray	INSYS Therapeutics	January 4, 2012	Sublingual spray approved for the treatment of breakthrough pain associated with cancer
Zetonna® (ciclesonide) nasal aerosol	Sunovion Pharmaceuticals	January 20, 2012	Corticosteroid nasal spray indicated for the treatment of allergic rhinitis symptoms (seasonal and perennial)

NEW FIRST-TIME GENERIC DRUG APPROVALS

Atorvastatin calcium tablet (Lipitor®)†
Launched: November 30, 2011

Eprosartan 600 mg tablet (Teveten®)
Launched: December 20, 2011

Felbamate 400 mg, 600 mg tablet (Felbatol®)
Launched: September 13, 2011

Felbamate oral suspension (Felbatol®)
Launched: December 20, 2011

Fenofibrate 48 mg, 145 mg tablet (Tricor®)
Approved: December 23, 2011
Launched: TBA

Levetiracetam extended-release 500 mg, 750 mg tablet (Keppra® XR)
Launched: September 14, 2011

Methylphenidate hydrochloride extended-release capsule (Ritalin® LA)
Launched: January 3, 2012

Morphine Sulfate extended-release 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg capsule (Kadian®)
Launched: November 10, 2011

Olanzapine oral tablet (Zyprexa®)
Launched: October 24, 2011

Olanzapine oral disintegrating tablet (Zyprexa® Zydis)
Launched: October 25, 2011

Olanzapine intramuscular injection (Zyprexa® IM Solution Reconstituted)
Launched: November 28, 2011

Tramadol hydrochloride extended-release 100 mg, 200 mg, 300 mg tablet (Ryzolt®)
Launched: December 30, 2011

†Ranbaxy has 180-day semi-exclusivity rights; Watson released an authorized generic on November 30, 2011.

PROJECTED FIRST-TIME GENERIC ENTRY

Modafinil (Provigil®)
April 2012

Clopidogrel (Plavix®)*
May 2012

Fluvastatin (Lescol®)
June 2012

Fluvastatin extended-release (Lescol® XL)
June 2012

Eszopiclone (Lunesta®)
July 2012

*Generic re-entry into market (will not have an exclusivity period due to original release in August 2006)

Glycemic Pattern Management

Background

In the United States, diabetes has become a growing epidemic with current prevalence estimates exceeding 8 percent.[1,2] This trend is expected to continue rising as the population of Medicare-eligible patients is projected to expand over the next several years. Unfortunately, diabetes is a progressive disease state and, despite advancements in pharmacologic therapy, appropriate glucose regulation remains a substantial challenge for many patients and providers. If patients' diabetes remains uncontrolled for a sustained amount of time, an unnecessary burden is placed upon the already strained healthcare system. The excessive expenditure is primarily derived from the cost of medications and diabetes-related complications, such as cardiovascular disease, microvascular impairment, and kidney failure.[3] In 2007 alone, the direct medical cost of diabetes was estimated to be more than $116 million in the United States.[2]

To combat these inflating healthcare costs, managed care organizations must develop innovative solutions to improve glucose regulation within their diabetic patient populations. One potential strategy to improve diabetes control and limit the risk of related complications for covered beneficiaries is promoting appropriate self-monitoring of blood glucose (SMBG). The American Diabetes Association (ADA) recommends that SMBG be performed at least three times a day in patients taking multiple daily injections of insulin.[4] The ADA guidelines also support that SMBG may be a useful guide to promote successful treatment in patients using less-frequent insulin injections, oral medications, or nutritional therapies.

For nearly 30 years, diabetic patients have been using portable electronic meters to monitor their blood glucose levels. However, this practice did not become a standard of care until 1993, when the Diabetes Control and Complications Trial demonstrated that maintaining near-normal glycemic levels could prevent or delay the long-term complications of Type 1 Diabetes Mellitus (T1DM).[5] Since then, the pharmaceutical device industry has developed a vast array of self-monitoring meters and downloadable software that offers patients and physicians the ability to more appropriately assess glycemic control. These tools allow patients to take responsibility for their disease state by providing them the ability to assess the effectiveness of their current therapeutic regimen on a daily basis. In addition, frequent monitoring of blood glucose helps patients develop a better understanding of what external factors, other than pharmacotherapy, contribute to their glucose levels (e.g., food, exercise, stress, etc).[6]

Patients who maintain comprehensive blood glucose records also give providers objective data to assess the true effectiveness of their pharmacologic treatment regimen. Hemoglobin A_{1c} (HbA_{1c}) levels are a good measurement of a patient's average blood glucose over a 90-day period, but they are unable to determine if a patient is experiencing both hypo- and hyperglycemic events on a regular basis. Additionally, HbA_{1c} levels are unable to distinguish between fasting, preprandial, and postprandial hyperglycemia; detect glycemic excursions; identify and monitor resolution of hypoglycemia; or provide immediate feedback to patients about the effect of food choices, activity, and medication on glycemic control.[7] Patients who routinely monitor their blood glucose levels have the potential to reduce their risk of developing costly macrovascular complications and generate a substantial amount of cost-savings for themselves and their health plan. The combination of clinical and financial benefits that are associated with SMBG make it an important facet to the overall management of diabetes and integral to the success of pharmacologic therapy.

Although SMBG provides a great benefit to the management of diabetes, few patients and physicians utilize this technology to its utmost potential. This is why a routine and structured SMBG regimen is only the starting point for appropriate glucose regulation. To truly optimize the effectiveness of diabetic treatment regimens and achieve successful glucose management, providers need to teach their diabetic patients realistic strategies to ensure the proper analysis of SMBG. One such strategy is the development of a comprehensive pattern management program.

Importance of Pattern Identification

Pattern management is a proactive and comprehensive tool used to improve glycemic management that considers all aspects of current diabetes therapy.[8] The process identifies recurring glycemic patterns that are potentially problematic for the patient. An all-inclusive pattern management program examines blood glucose values in addition to food intake, activity levels, doses of insulin and/or other glucose-lowering medication, illness, stress, and any other factor that may influence a patient's glucose level. Pattern management is generally the most effective for patients treated with insulin, but all patients with diabetes can benefit from a more intensive approach to glycemic control. Through the use of pattern management, patients learn to analyze several days of glucose readings, recognize potential problems, identify the cause of the pattern, and work with their physician to resolve negative patterns proactively, rather than treating each individual glucose measurement as a separate encounter. This therapeutic strategy incorporates a two- to five-day retrospective analysis of blood glucose readings to help patients and providers easily identify individualized trends in glucose regulation.

Critics of diabetes pattern management believe that this approach to glycemic regulation has become outdated as many patients using multiple-dose insulin therapy utilize a sliding-scale algorithm for bolus doses. However, it can be argued that pattern management becomes a more important aspect of a patient's therapeutic treatment plan as their insulin regimen becomes more complicated. Sliding-scale, or supplemental, insulin therapy is a method of adjusting insulin to correct the blood glucose at a particular moment in time. This, however, does not resolve the underlying problem and only acts as a quick fix rather than addressing the cause of the variant glucose readings. Pattern management gives patients and providers the necessary information to make informed decisions regarding a patient's individualized glucose regulation and reduce the risk of hypo- and hyperglycemic episodes.

To appropriately incorporate glycemic pattern management into therapeutic practice, it is essential for physicians to empower their patients to take responsibility for their disease state. Pattern management requires a meticulous record of multiple-daily glucose readings, insulin doses, carbohydrate intake, physical activity, illness, and stress level to be the most effective. It is difficult for many patients to record such a comprehensive diabetes diary, especially if there is a lack of appreciation for the therapeutic purpose. However, once a patient is properly trained and educated on the process, patients can then analyze a series of blood glucose readings, taken at the same time each day, to determine if they are experiencing hypo- or hyperglycemic patterns over the course of several days. This allows the patients to identify what could be contributing to the negative patterns and, with their physician, modify their treatment regimen and/or eating habits to ensure the prompt correction of potentially problematic patterns.

continued

"To appropriately control [diabetes], a multifaceted approach to treatment is often required for the greatest chance of success, with an emphasis placed on using treatment options aimed at attaining blood sugar goals, slowing progression, and reducing complications."

Pattern management involves five basic steps[7,9]:

1. Establish pre- and postprandial glucose targets
2. Obtain data on blood glucose levels, carbohydrate intake, medication administration (type, dosage, timing), activity levels, schedule, and physical/emotional stress
3. Analyze data to identify patterns and assess for influencing factors
4. Implement appropriate actions
5. Perform ongoing SMBG to assess the impact of any therapeutic changes

Barriers to Appropriate SMBG

In order for a pattern management program to be effective, patients must follow a structured blood glucose monitoring schedule. Unfortunately, this is a difficult task for many diabetic patients as there are several patient-related barriers inhibiting routine testing. Many patients do not believe that SMBG is a necessary part of their diabetes therapy. This skepticism can be derived from a variety of factors but is usually directly related to a lack of patient education. Many physicians do not spend a sufficient amount of time discussing the importance of SMBG with their patients, which results in inadequate testing practices. Additionally, pain at lancing site, cost of supplies, and forgetfulness also heavily contribute to SMBG adherence problems.

Another major barrier to the widespread implementation of appropriate monitoring is the foreseen lack of actionability of the generated results by both patients and providers. Patients do not particularly enjoy testing their blood glucose multiple times a day as it is an uncomfortable, and often painful, experience. However, it is difficult for physicians to develop clinical conclusions and modify therapy based upon random and infrequent glucose measurements. Even for patients who strictly adhere to their self-management protocol, physicians generally do not devote a sufficient amount of time to adequately analyze the results and determine individualized glycemic patterns. Therefore, the majority of physicians treating diabetic patients base their clinical decision making solely on the patient's HbA_{1c} level. While this may be appropriate for some patients, HbA_{1c} levels do not accurately portray the full spectrum of glucose regulation. For this reason, making SMBG measurements routinely available and easy for patients and physicians to interpret will provide a more realistic depiction of a patient's individual glucose regulation and allow providers to accurately modify therapeutic strategies in diabetic patients. Pattern management may provide a solution to the current disregard for routine blood glucose monitoring.

A comprehensive pattern management program also has the ability to minimize the clinical inertia associated with optimizing insulin therapy. All individuals with T1DM, and eventually most with Type 2 Diabetes Mellitus (T2DM), will require insulin therapy.[9] These patients represent the highest risk of experiencing hypoglycemic episodes, which can have a substantial negative impact on morbidity. Unfortunately, hypoglycemia acts as a deterrent for intensifying therapy for diabetics. Due to the progressive nature of the disease, it is important to continue to change and intensify therapy to appropriately manage the condition. Hesitation by physicians to intensify insulin therapy is often caused by a concern that their patient will have hypoglycemic episodes. Pattern management has the potential to reduce this clinical inertia that prevents the intensification of diabetes treatment and make SMBG values actionable. By appropriately utilizing pattern management, physicians will be able to identify trends in their patients' glucose regulation and proactively modify therapy to ensure the elimination of hypoglycemic patterns.

Implications to Managed Care

As the United States healthcare system is increasingly becoming a more accountable industry, managed care

organizations are faced with the tremendous responsibility of accepting liability for both the financial and clinical outcomes of their covered beneficiaries. With the recent healthcare reform initiatives being mandated by the federal government, the driving factors for managed care decision making are transforming from the traditional cost-containment strategies of previous years to improving quality outcomes. Health plans are now faced with the daunting task of improving clinical quality of treatment while simultaneously controlling the continually escalating healthcare expenditures being observed nationally.

Patients with diabetes are potentially the most difficult population to manage from a clinical and financial standpoint. Diabetes is a highly prevalent and complicated disease that affects numerous organ systems throughout the body.[10] It has an enormous impact on healthcare spending, a majority of which results from the debilitating and costly complications that arise as a result of inadequate glucose control.[11] To appropriately control this disease, a multifaceted approach to treatment is often required for the greatest chance of success, with an emphasis placed on using treatment options aimed at attaining blood sugar goals, slowing progression, and reducing complications.

One strategy to improve the clinical outcomes in patients with diabetes, while simultaneously reducing unnecessary healthcare utilization, is to promote appropriate SMBG and pattern management. Unfortunately, there has been an ongoing debate among healthcare professionals regarding the effectiveness of SMBG in reducing a patient's HbA_{1c} levels, particularly in patients with T2DM. In response to this, several clinical studies have been conducted with the goal of quantifying the relationship that SMBG has on HbA_{1c} values. In the Diabetic Outcomes in Veterans Study (DOVES), the effect of intensive short-term SMBG in insulin-treated patients was examined. The participants in the study tested their blood glucose four times daily for an eight-week period. The result of the study was a significant decrease in patients' HbA_{1c} that was visible at four weeks, maximized at eight weeks, and was still evident after 52 weeks when the patients had returned to their baseline level of monitoring.[12]

In 2011, a study was published in *Diabetes Care* that analyzed the effectiveness of structured blood glucose testing in poorly controlled, noninsulin-treated type 2 diabetics.[13] This study demonstrated statistically significant reductions in HbA_{1c} levels in the structured testing group when compared to the active control group, -1.2% vs. -0.9% respectively (p-value = 0.04). This study also evaluated potential reasons for the reduction in HbA_{1c} and determined that patients using intensified SMBG were three times more likely to schedule office visits and receive medication modifications than patients utilizing standard SMBG. This increase in physician visits and medication changes suggest that when patients retain structured SMBG records, physicians can interpret the results and intervene in a timely fashion.

Pattern management is a perfect tool to assist patients and physicians in developing structured SMBG records that allow for the simple identification of clinically relevant patterns in patients' glucose readings. The resulting therapeutic modifications can then lead to better control of a patient's disease state, potentially decrease future hospitalizations, reduce the risk of diabetes-related complications, and decrease the economic burden of diabetes on the U.S. healthcare system.

References

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CDMI PEER REVIEW PROCEDURE

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The procedure is as follows:

- ☐ The manuscript is initially screened by the editor-in-chief and the executive editor. Works deemed unsuitable for our publication will be returned to the authors with a detailed letter explaining our reasons.
- ☐ If potentially acceptable, the manuscript will then be distributed to at least two outside reviewers of the executive editor's choosing. Our reviewers are extensively trained in medical literature analysis and their expertise has proven to be a valuable asset. The executive editor may also decide to submit the manuscript to an expert in the associated field.
- ☐ The comments from the reviewers will then be compared. Manuscripts that pass the peer-review process will undergo a final review by the editorial committee. If a manuscript passes this final stage, it will be added to the CDMI database and be a candidate for publication. Rejected manuscripts will then be returned to the author with a detailed letter explaining the reason for rejection. If there is still interest in the manuscript but editing is required, the reviewer's comments will be assessed by the executive editor. If the executive editor agrees with the comments and recommendations, the notes will be forwarded back to the author for appropriate modification of material.
- ☐ After manuscript revision, the work will be re-distributed to the appropriate reviewers for evaluation. If further modification is required, the manuscript will be sent back to the author for additional editing. Upon meeting the reviewer's requirements, the work will be presented to the editorial committee for a final assessment. Upon approval of the editorial committee, the manuscript is then added to the CDMI database and is a candidate for publication.
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- ☐ After approval of the manuscript and with the intent of CDMI to publish, the author will then be notified and compensated appropriately.

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To inspire the reviews to be as critical and honest as possible, CDMI does not divulge the names of the reviewers of specific manuscripts. It is our impression that confidential reviewers are ideal for this procedure because they can feel free to be more candid and rigorous with their recommendations. Comments that may be hostile, belligerent, or unreasonable will not be transmitted back to the author. We will not withhold the author's identity from the reviewers unless otherwise requested by the author.

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 human relevance could not be ruled out by clinical or nonclinical studies. 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). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[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:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution 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 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).

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. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. 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 could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications]*. In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in 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. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum 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, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and 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. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there were 7 cases of pancreatitis among Victoza®-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza® were reported as acute pancreatitis and two cases with Victoza® 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. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, 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® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues *[see Adverse Reactions]*. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: 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® was evaluated in a 52-week monotherapy trial and in four 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza® 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza® 1.2 mg, Victoza® 1.8 mg or placebo. *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 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. 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. Tables 1 and 2 summarize the adverse events reported in ≥5% of Victoza®-treated patients in the five controlled trials of 26 weeks duration or longer.

Table 1: Adverse events reported in ≥ 5% of Victoza®-treated patients or ≥5% of glimepiride-treated patients: 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Event Term	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper Respiratory Tract Infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary Tract Infection	6.0	4.0
Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4
Hypertension	3.0	6.0

Table 2: Adverse events 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 Event Term	(%)	(%)	(%)
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 Event Term	(%)	(%)	(%)
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 Event Term	(%)	(%)	(%)
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 Event Term	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Decreased Appetite	9.3	1.1
Anorexia	9.0	0.0
Headache	8.2	4.6
Constipation	5.1	1.1
Fatigue	5.1	1.7

Gastrointestinal adverse events: In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. *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 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 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the 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 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the 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 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 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 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.9 vs. 0.6 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 clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 3). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 3: 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 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

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:** 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.

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. 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 on request.

For information about Victoza® contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, 1–877-484-2869

Date of Issue: January 2010
Version: 1

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

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VICTOZA®
liraglutide (rDNA origin) injection

Victoza® made a deep impact in its first year.

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- ✓ Over **160,000** patients started taking Victoza®*
- ✓ VictozaCare™ provides patients the support they need to get started

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Indications and usage

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution 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 insulin has not been studied.

Important safety information

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 human relevance could not be ruled out by clinical or nonclinical studies. 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). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

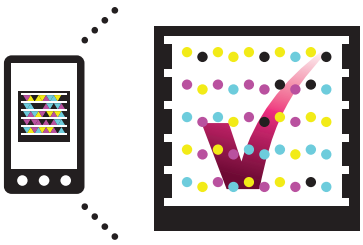
The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated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

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

Victoza® should be used with caution in patients with renal impairment and in patients with hepatic impairment.

Please see brief summary of Prescribing Information on adjacent page.

*IMS Health Inc. LifeLink Longitudinal Prescription Database (LRx)™, December 2010.



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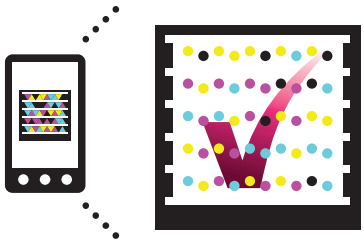

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